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(54) **Naphthalene derivatives, processes for preparing the same, and synthetic intermediates therefor**

Naphthalinderivate, ihre Herstellungsverfahren und synthetische Zwischenprodukte dafür

Dérivés de naphtalène, procédés pour leur préparation et des produits intermédiaires appropriés

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US-A- 4 661 596

- **TETRAHEDRON, (INCL. TETRAHEDRON REPORTS) vol. 30, no. 15, 1974, OXFORD GB pages 2431 - 2436 D.N. REINHOUDT ET AL. 'Novel route for the synthesis of benzo(b)thiepins.'**

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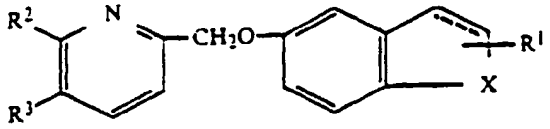
Description

The present invention relates to a novel naphthalene derivative having an antiasthmatic activity, processes for preparing the same, and synthetic intermediate therefor.

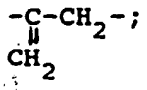
Although there has been known as a naphthalene derivative having a nitrogen-containing 6-membered heterocyclic group at the 1-position, 1-(5-methyl-2 (1H)-pyridon-3-yl)-naphthalene [cf. Bulletin of The Chemical Society of Japan, Vol. 41, 165-167 (1968)], a pharmaceutical use and activities thereof have never been disclosed. On the other hand, many antiasthmatics have been known, but conventional antiasthmatics have various deficits, for example they do not show sufficient inhibitory action on bronchoconstriction, or they cannot overcome serious side effects on *inter alia* the heart.

Also US-A-4 661 596 discloses various quinolinyl (or pyridinyl) methoxy substituted naphthalene compounds as antiallergic agents. In particular this specification discloses a compound having the formula:



wherein

X is $-CH_2CH_2-$, $-CH=CH-$.



R is hydrogen or loweralkyl;

R^1 is hydroxy, amino, loweralkyl sulfonamido, perfluoro loweralkyl sulfonamido, or OR;

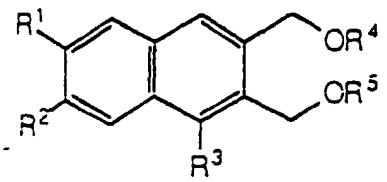
R^2 is hydrogen or loweralkyl;

R^3 is hydrogen or loweralkyl; or

R^2 and R^3 taken together form a benzene ring; and the dotted line represents an optional double bond; and the pharmaceutically acceptable salts thereof.

Under such circumstances, the present inventors have studied intensively, and have found novel naphthalene compounds having antiasthmatic activity, of which structures are different from those of the conventional compounds having antiasthmatic activity.

An object of the invention is to provide novel naphthalene derivatives having antiasthmatic activity of the formula (I):



[I]

wherein R^1 and R^2 are the same or different and are (1) hydrogen atom, (2) hydroxy group, (3) a cyclo-C_{3-6} alkyloxy group, (4) a C_{1-6} alkoxy group which may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group and phenyl group, or (5) both combine each other to form a C_{1-6} alkylenedioxy group, R^3 is a nitrogen-containing 6-membered heterocyclic group which may optionally be substituted by a group selected from a halogen atom, an alkoxy group and an alkyl group, in which these alkoxyl group and alkyl group may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{2-6} alkenyl group, cyano group, carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aminocarbonyl group, a di-C_{1-6} alkylamino group, a C_{2-6} alkanoyl group, phenyl group, furyl group, tetrahydrofuryl group and oxazolyl group, and groups of the formulae: $-OR^4$ and $-OR^5$ are the same or different and are a protected or unprotectea hydroxy group, or a pharmaceutically acceptable salt thereof.

Another object of the invention is to provide processes for preparing the compounds (I) or a pharmaceutically acceptable salt thereof.

The other object of the invention is to provide closely related synthetic intermediates therefor.

The desired compounds (I) of the present invention and pharmaceutically acceptable salts thereof have potent bronchodilating activity, and are useful as medicines in the prophylaxis and treatment of asthma. For instance, the desired compounds (I) show potent inhibitory activity on bronchoconstriction e.g. 3 to 100 times stronger than that of theophylline, without showing any side effects on heart.

Suitable examples of the desired compounds [I] of the present invention are the compounds of the formula [I], wherein R3 is pyridyl group, N-oxypyridyl group, 2(1H)-pyridonyl group, 4,5-dihydro-3(2H)-pyridazinonyl group or 3 (2H)-pyridazinonyl group, which may be substituted by a halogen atom (e.g. fluorine), or 2-alkoxypyridyl group or N-alkyl-2(1H)-pyridonyl group, in which said alkoxy group and alkyl group may optionally be substituted by a group selected from hydroxy group, a lower alkoxy group, a lower alkoxy-lower alkoxy group, a lower alkylthio group, a lower alkenyl group, cyano group, carboxyl group, a lower alkoxycarbonyl group, carbamoyl group, a di-lower alkylamino group, a lower alkanoyl group, phenyl group, furyl group, tetrahydrofuryl group and oxazolyl group.

Other examples of the desired compounds [I] of the present invention are the compounds of the formula [I], wherein R^1 and R^2 are (1) hydrogen atom, (2) hydroxy group, (3) a cyclo-lower alkyloxy group, or (4) a lower alkoxy group which may optionally be substituted by a group selected from hydroxy group, a lower alkoxy group, a lower alkoxy-lower alkoxy group, a lower alkoxycarbonyl group and phenyl group, or (5) both combine each other to form a lower alkylenedioxy group.

The pharmaceutically preferable compounds [I] are the compounds of the formula [I], wherein R^1 and R^2 are the same or different and are a lower alkoxy group, and R^3 is pyridyl group, N-alkyl-2(1H)-pyridonyl group or N-(lower alkoxy-lower alkyl)-2(1H)-pyridonyl group.

Among the desired compounds [I] of the present invention, groups of the formulae: $-OR^4$ and/or $-OR^5$ are either hydroxy group or a hydroxy group protected by any pharmaceutically acceptable groups. The hydroxy-protecting group may be any ones which are removed by hydrolysis in living body, and do not produce any harmful side products. Suitable examples of the protected hydroxy group are hydroxy groups protected by a lower alkanoyl group or a lower alkyl group.

The desired compounds [I] of the present invention can be used as a medicine either in the free form or in the form of pharmaceutically acceptable salt thereof. For example, since the desired compounds [I] have a nitrogen-containing 6-membered heterocyclic group at the 1-position of the naphthalene nucleus, they can be used in the form of an organic or inorganic acid addition salt thereof. Further, when the desired compounds [I] have a substituent such as carboxyl group on the nitrogen-containing 6-membered heterocyclic group, they can be used in the form of a basic salt thereof.

The pharmaceutically acceptable salts are, for example, salts with inorganic acids (e.g. hydrochloride, sulfate, hydrobromide), salts with organic acids (e.g. acetate, fumarate, oxalate), alkali metal salts (e.g. sodium salt, potassium salt) or alkaline earth metal salts (e.g. calcium salt).

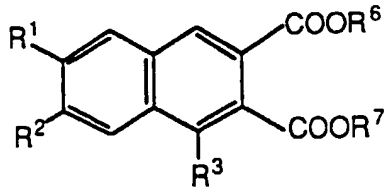
The desired compounds [I] of the present invention and pharmaceutically acceptable salts thereof can be administered either orally or parenterally, and administered in the form of conventional pharmaceutical preparations such as tablets, granules, capsules, powder, injection forms and inhalants.

The dosage of the desired compounds [I] of the present invention and pharmaceutically acceptable salts thereof varies depending on administration route, age, weight and conditions of the patients, but it is usually in the range of about 0.01 to 30 mg/kg/day, preferably about 0.1 to 10 mg/kg/day.

According to the present invention, the desired compounds [I] of the present invention can be prepared by any one of the following Process A to Process D.

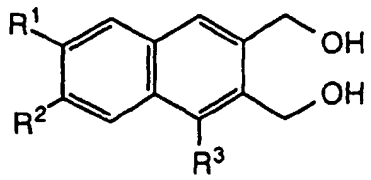
Process A

The desired compounds [I] of the present invention can be prepared by subjecting a compound of the formula [II]:



[II]

wherein R^1 and R^2 are the same or different and are hydrogen atom, hydroxy group, a cyclo-lower alkyloxy group, a substituted or unsubstituted lower alkoxy group, or both combine each other to form a lower alkylenedioxy group, R^3 is a substituted or unsubstituted nitrogen-containing 6-membered heterocyclic group, and groups of the formulae: $-COOR^6$ and $-COOR^7$ are a free carboxyl group or esterified carboxyl group, or an internal anhydride thereof, to reduction to give a compound of the formula [I-a]:

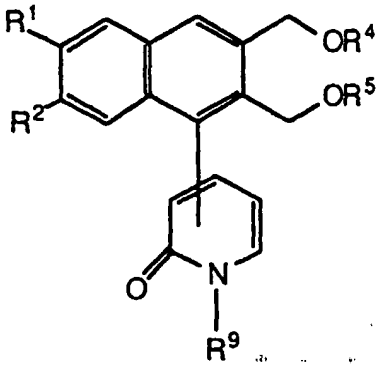


[I-a]

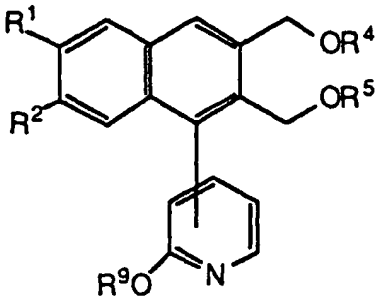
wherein the symbols are the same as defined above, if necessary, followed by protecting the 2- and/or the 3-hydroxymethyl moieties.

Process B

Among the desired compounds [I] of the present invention, the compounds of the formulae [I-c] and [I-d]:

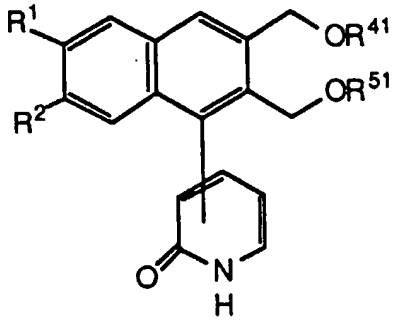


[I-c]



[I-d]

wherein R^9 is a substituted or unsubstituted lower alkyl group, and the other symbols are the same as defined above, can be prepared by reacting a compound of the formula [I-b_1]:

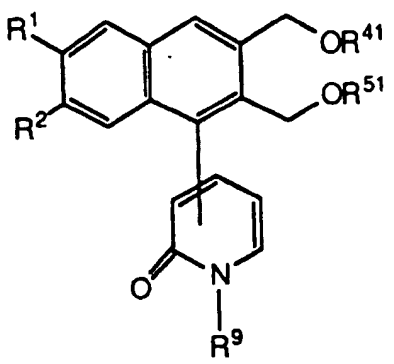


[I-b_1]

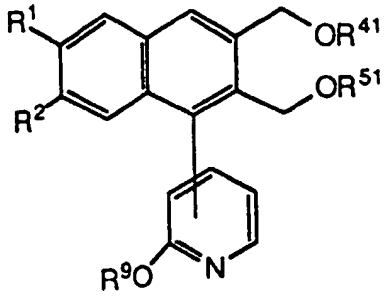
wherein groups of the formulae: -OR^{41} and -OR^{51} are protected or unprotected hydroxy group, and the other symbols are the same as defined above, with a compound of the formula [III]:

$$X\text{-}R^9 \qquad \text{[III]}$$

wherein X is a halogen atom and R^9 is the same as defined above, to give compounds of the formulae [I-c_1] and [I-d_1]:



[I-c_1]

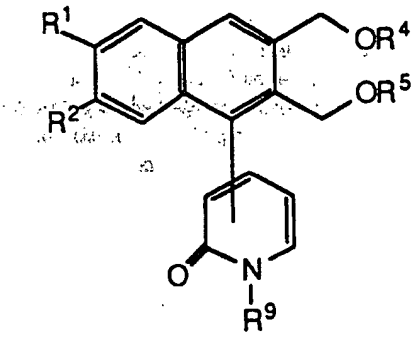


[I-d_1]

wherein the symbols are the same as defined above, and when the groups of the formulae: -OR^{41} and/or -OR^{51} are a protected hydroxy group, if necessary, followed by removing the protecting group for said hydroxy groups, and further if necessary, by protecting again the 2- and/or 3-hydroxymethyl moieties.

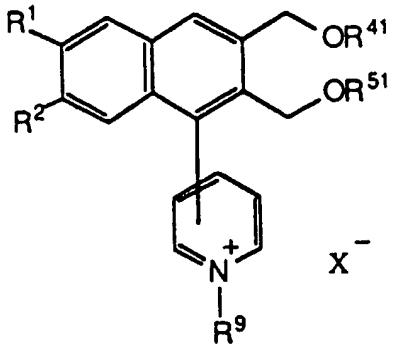
Process C

Among the desired compounds [I], the compound of the formula [I-c]:



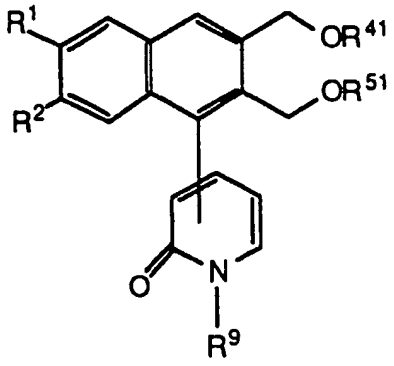
[I-c]

wherein the symbols are the same as defined above, can also be prepared by subjecting a compound of the formula [I-e_1]:



[I-e_1]

wherein the symbols are the same as defined above, to oxidation to give a compound of the formula [I-c_1]:

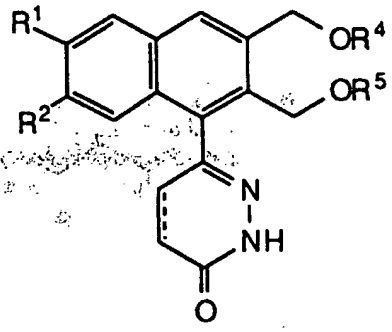


[I-c$_1$]

wherein the symbols are the same as defined above, when the groups of the formulae: -OR^{41} and -OR^{51} are a protected hydroxy group, if necessary, followed by removing the protecting group for said hydroxy groups, and further if necessary, by protecting again the 2- and/or 3-hydroxymethyl moieties.

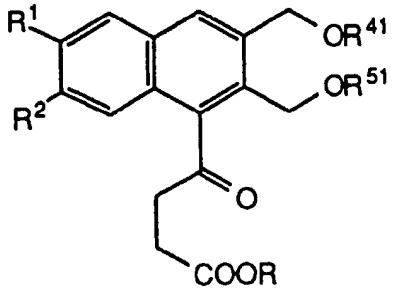
Process D

Among the desired compounds [I], the compound of the formula [I-h]:



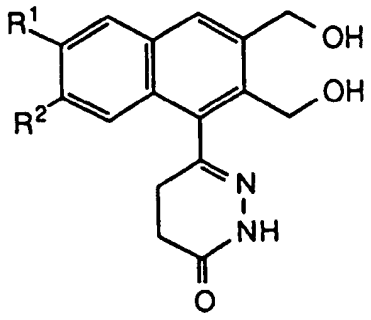
[I-h]

wherein the dotted line means single bond or double bond, and the other symbols are the same as defined above, can be prepared by reacting a compound of the formula [IV]:



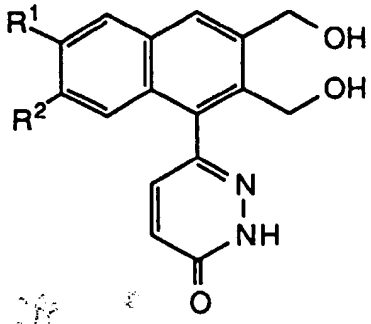
[IV]

wherein the group of the formula: -COOR is a free carboxyl group or an esterified carboxyl group, and the other symbols are the same as defined above, with hydrazine to give a compound of the formula [I-f]:



[I-f]

wherein the symbols are the same as defined above, if necessary, followed by subjecting the compound [I-f] to oxidation to give a compound of the formula [I-g]:



[I-g]

wherein the symbols are the same as defined above, and if necessary, further by protecting the 2- and/or 3-hydroxymethyl moieties of the compound [I-f] or [I-g].

These processes A to D can be carried out as follows.

Process A

The reduction reaction of the starting compound [II] or an internal anhydride thereof can be carried out using a suitable reducing agent in a suitable solvent. The esterified carboxyl group of the starting compound [II] may be any one which can be converted into hydroxymethyl group by the reduction reaction, and includes, for example, a lower alkoxycarbonyl group. The reducing agent may be selected according to the types of R^6 and R^7. For instance, when R^6 and/or R^7 are an ester residue, the reducing agent is, for example, lithium aluminum hydride, sodium bis(methoxyethoxy)aluminum hydride, sodium borohydride, and among which sodium bis(methoxyethoxy)aluminum hydride is preferable. On the other hand, when R^6 and/or R^7 are hydrogen atom, lithium aluminum hydride is preferably used as a reducing agent. Further, the internal anhydride of the compound [I] can be prepared by subjecting the compound [I] wherein R^6 and R^7 are hydrogen atom, to internal dehydration reaction. The reduction of said internal anhydride compound is carried out under the same conditions as the reduction reaction of the compound [II] wherein R^6 and/or R^7 are hydrogen atom. These reduction reactions can be carried out in a suitable solvent such as ethers (e.g. tetrahydrofuran, diethyl ether, dioxane) under cooling or heating.

Process B

The condensation reaction between the compounds [I-b_1] and [III] can be carried out in the presence of a base in a suitable solvent. The base includes, for example, sodium hydride, lithium hydride, lithium diisopropylamide, potassium bis-(trimethyl)amide, and the like, and the solvent includes, for example, dimethylformamide.

The desired compounds [I-c] and [I-d] obtained in Process B can be separated by a conventional method such as chromatography (e.g. silica gel chromatography).

Process C

The oxidation reaction of the compound [I-e_1] can be carried out in a suitable solvent by a conventional method.

The oxidizing agent includes, for example, dicyanodichloroquinone, potassium ferricyanide, among which potassium ferricyanide is preferable. The solvent may be any one which does not affect the reaction, and includes, for example, dioxane, water, methanol and ethanol. The reaction is preferably carried out under cooling or at room temperature.

Process D

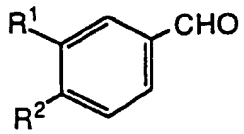
The reaction between the compound [IV] and hydrazine can be carried out in a suitable solvent. Hydrazine is preferably hydrazine hydrate. The solvent may be any one which does not affect the reaction, and includes, for example, methanol, ethanol, tetrahydrofuran and dimethylformamide. The reaction is preferably carried out with warming or heating. When the compound [IV], wherein the 2- and/or 3-positions are a protected hydroxy group, is used in this reaction, the said protecting groups for hydroxy group are removed simultaneously.

The oxidation of the compound [I-f] can be carried out using an oxidizing agent in a suitable solvent. The oxidizing agent is preferably dicyanodichloroquinone. The solvent may be any one which does not affect the reaction, for example, dioxane, methanol, ethanol and water. The reaction is preferably carried out under cooling or at room temperature.

In the above Processes B and C, when the groups of the formulae: $-OR^{41}$ and/or $-OR^{51}$ are a protected hydroxy group, the removal of the said protecting group from the products can be carried out by a conventional method, which is selected according to the types of the protecting groups to be removed, for example, hydrolysis, acid treatment reduction. Moreover, in the above Processes A to D, the protection of the 2- and/or 3-hydroxymethyl moieties can be carried out by a conventional method, for example, by subjecting the OH-unprotected product to condensation reaction with a reactive derivative of the protecting group corresponding to R^4 and R^5, e.g. acid anhydride of a lower alkanoic acid, acid halide, a lower alkyl halide. The reaction is preferably carried out in the presence or absence of a basic compound (e.g. triethylamine, pyridine, dimethylaminopyridine, sodium hydride) in a suitable solvent (e.g. methylene chloride) or without a solvent. Since the 3-hydroxymethyl moiety is more reactive than the 2-hydroxymethyl moiety, when a reactive derivative of the protecting group is used in an equimolar amount to the OH-unprotected product, there are mainly obtained the products wherein only the 3-hydroxymethyl moiety is protected. When the reactive derivative of the protecting group is used in an amount of two moles or more to one mole of the OH-unprotected product, there can be obtained the products wherein both the 2- and 3-positions are duly protected.

Moreover, the desired compounds of the present invention are mutually converted, for example, the desired compound [I] having N-oxypyridyl group at the 1-position, can be prepared by subjecting the desired compound [I] having pyridyl group at the 1-position, to oxidation reaction. The desired compound [I-b] having 2(1H)-pyridonyl group at the 1-position, can be prepared by reacting the compound [I] having N-oxypyridyl group at the 1-position, with an acid anhydride, followed by treating the product with a base. The compound [I-e] having N-substituted pyridyl group at the 1-position can be prepared by introducing a corresponding substituent on the N-position of the compound [I] having pyridyl group at the 1-position, by a conventional method.

The starting compound [II] of the present invention is a novel compound, and can be prepared by treating a benzaldehyde compound of the formula [V]:

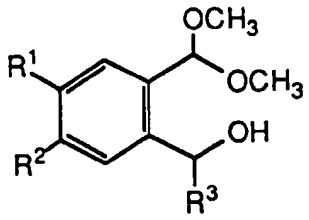


[V]

wherein R^1 and R^2 are the same as defined above, with a halogen (e.g. bromine), followed by reacting the obtained 6-halogenobenzaldehyde compound with methyl ortho-formate in the presence of an acid catalyst (e.g. strong acidic resin), and further, by reacting the product with an aldehyde compound of the formula [VI]:

[VI]

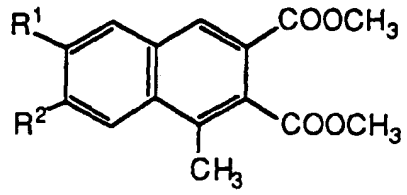
wherein R3 is the same as defined above, in the presence of a basic compound (e.g. n-butyl lithium) to give a compound of the formula [VII]:



[VII]

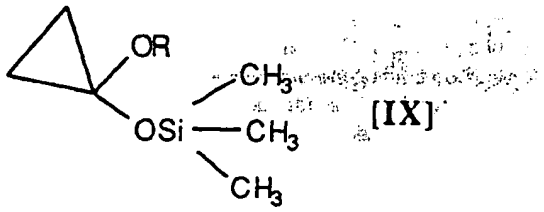
wherein R^1, R^2 and R^3 are the same as defined above, followed by condensing the product with a maleic acid diester, if necessary, by removing the ester residue from the condensation reaction product.

The starting compound [IV] of the present invention is also a novel compound, and can be prepared by reducing a compound of the formula [VIII]:



[VIII]

wherein R1 and R^2 are the same as defined above, which is prepared according to the process for preparing the starting compound [II], with for example lithium aluminum hydride, followed by protecting the hydroxy group of the obtained 2,3-bis(hydroxymethyl) compound, oxidizing the 1-methyl group of the product by a conventional method to convert it into an aldehyde group, and reacting the obtained aldehyde compound with a compound of the formula [IX]:



[IX]

wherein R is the same as defined above, and finally oxidizing the product with an oxidizing agent, such as pyridinium chlorochromate.

The starting compounds [II] or [IV] can mutually be converted. The mutual conversion of the starting compounds [II] can be carried out in the same manner as the mutual conversion of the desired compounds [I]. Besides, among the starting compounds [II] and [IV], the compounds, wherein R^1 and/or R^2 are benzyloxy group, can be converted into the compounds wherein R^1 and/or R^2 are hydroxy group by a conventional reduction reaction, which are further converted into the compounds wherein R^1 and/or R^2 are a cyclo-lower alkoxy group or a substituted or unsubstituted lower alkoxy group by protecting said hydroxy groups by a conventional method.

Throughout the present description and the claims, the alkyl group and alkoxy group are ones having 1 to 10 carbon atoms, preferably 1 to 8 carbon atoms, respectively, and the lower alkyl group, the lower alkoxy group and the lower alkylene group are ones having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, respectively. The lower alkanoyl group is ones having 2 to 6 carbon atoms, preferably 2 to 5 carbon atoms, and the cyclo-lower alkyl group is ones having 3 to 6 carbon atoms, preferably 5 carbon atoms.

Examples

The present invention is illustrated in more detail by the following Examples and Reference Examples, but should not be construed to be limited thereto.

Example 1

To tetrahydrofuran (25 ml) is added a 3.4 M solution of sodium bis(methoxyethoxy)aluminumhydride in toluene (18.0 ml), and the mixture is cooled to -10°C. To the mixture is added dropwise a suspension of 1-(4-pyridyl)-2,3-bis (methoxycarbonyl)-6,7-diethoxynaphthalene (10.0 g) in tetrahydrofuran (25 ml) over a period of time for 15 minutes.

The reaction solution is warmed, and stirred under ice-cooling for 1.5 hour, and thereto is added 15 % aqueous sodium hydroxide solution (3.7 ml). To the reaction mixture are added water and methylene chloride, and the insoluble materials are removed by filtration. The filtrate is extracted with methylene chloride, and the extract is washed, dried, and concentrated to give 1-(4-pyridyl)-2,3-bis(hydroxymethyl)-6,7-diethoxynaphthalene (7.89 g).

Yield: 91.1 %
M.p. 159 - 161°C

Example 2

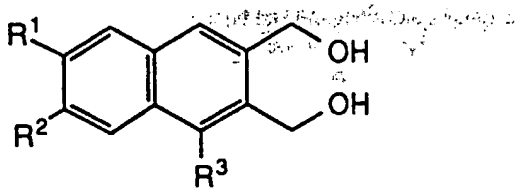
A solution of 1-(4-pyridyl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene (2.0 g) in tetrahydrofuran (50 ml) is added dropwise to a suspension of lithium aluminum hydride (100 mg) in tetrahydrofuran (20 ml) at -20°C. The mixture is stirred under ice-cooling for one hour, and thereto are added water (0.1 ml) and 15 % aqueous sodium hydroxide solution (0.1 ml). Ten minutes thereafter, water (0.3 ml) is added to the reaction mixture, and the mixture is stirred at room temperature for one hour. The insoluble materials are removed by filtration on celite, and the filtrate is concentrated. The residue is recrystallized from a mixture of ethyl acetate and diethyl ether (1:1) to give 1-(4-pyridyl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene (1.35 g).

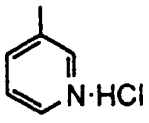
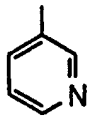
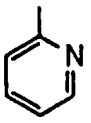
Yield: 80 %
M.p. 118 - 120°C

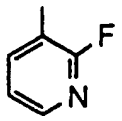
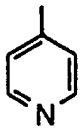
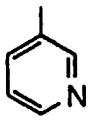
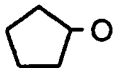
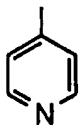
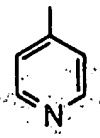
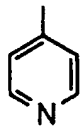
Example 3

The corresponding dicarboxylic acid methyl ester compounds are treated in the same manner as in Example 2 to give the compounds of Table 1.

Table 1



Ex. No.	R^1	R^2	R^3	Physical Properties
3-(1)	H	H		M.p. 183-185°C
3-(2)	CH_3O	CH_3O		M.p. 155-157°C
3-(3)	CH_3O	CH_3O		M.p. 124-125°C

3-(4)	CH_3O	CH_3O		M.p. 173-175°C
3-(5)	CH_3CH_2O	CH_3O		M.p. 206-208°C
3-(6)	-O-CH_2-O-			M.p. 208-210°C
3-(7)	CH_3O			Powder
3-(8)	CH_3CH_2O	$CH_3(CH_2)_2O$		M.p. 131-133°C
3-(9)	CH_3CH_2O	$CH_3(CH_2)_4O$		M.p. 101-104°C

Example 4

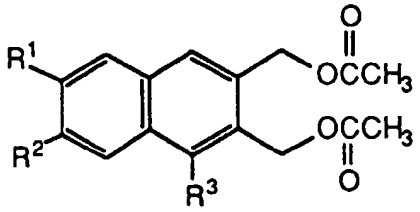
1-(4-Pyridyl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene (6.50 g) is dissolved in methylene chloride (50 ml), and thereto are added dropwise acetic anhydride (6.12 g) and triethylamine (6.06 g) under ice-cooling, and the mixture is stirred at room temperature overnight. The mixture is diluted with methylene chloride, and washed with water, dried and concentrated. The resulting residue is recrystallized from a mixture of ethyl acetate and hexane to give 1-(4-pyridyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (7.45 g).

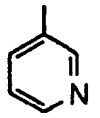
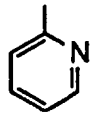
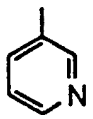
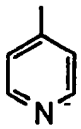
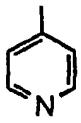
Yield: 93.6 %
M.p. 161 - 163°C

Example 5

The corresponding bis(hydroxymethyl)-type compounds are treated in the same manner as in Example 4 to give the compounds of Table 2.

Table 2



Ex. No.	R^1	R^2	R^3	Physical properties
5-(1)	CH_3O	CH_3O		M.p. 112-114°C
5-(2)	CH_3O	CH_3O		Oil
5-(3)	-O-CH_2-O-			M.p. 130-132°C
5-(4)	CH_3CH_2O	CH_3O		M.p. 145-146°C
5-(5)	CH_3CH_2O	CH_3CH_2O		M.p. 115-116°C

Example 6

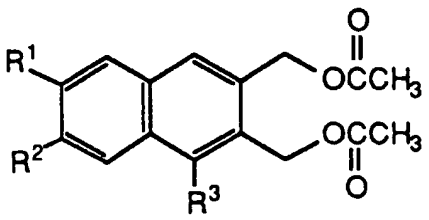
To a solution of 1-(4-pyridyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (5.6 g) in methylene chloride (150 ml) is added m-chloroperbenzoic acid (2.3 g) at room temperature, and the mixture is stirred overnight. The reaction solution is washed successively with aqueous sodium hydrogen carbonate solution and a saturated sodium chloride solution, and dried over magnesium sulfate, and concentrated. The resulting residue is crystallized from diethyl ether to give 1-(N-oxy-4-pyridyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (4.5 g).

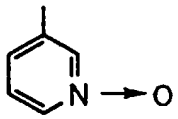
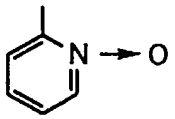
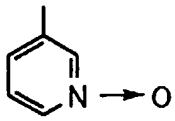
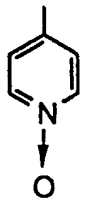
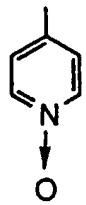
Yield: 78 %
M.p. 210 - 212°C

Example 7

The corresponding pyridyl-type compounds are treated in the same manner as in Example 6 to give the compounds of Table 3.

Table 3



Ex. No.	R^1	R^2	R^3	Physical properties
7-(1)	CH_3O	CH_3O		Used in the next reaction without purification
7-(2)	CH_3O	CH_3O		M.p. 137-139°C
7-(3)	-O-CH_2-O-			Used in the next reaction without purification
7-(4)	CH_3CH_2O	CH_3O		Used in the next reaction without purification
7-(5)	CH_3CH_2O	CH_3CH_2O		M.p. 158-159°C

Example 8

To 1-(N-oxy-4-pyridyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (4.5 g) is added acetic anhydride (20

ml), and the mixture is refluxed for 8 hours. The reaction solution is concentrated, and the resulting residue is dissolved in methanol (15 ml), and thereto is added conc. aqueous ammonia solution (0.8 ml) under ice-cooling. The mixture is warmed to room temperature, and stirred for 20 minutes. The precipitated crystals is collected by filtration, and washed with methanol to give 1-(2(1H)-pyridon-4-yl)-2,3-bis(acetoxymethyl)-6-7-dimethoxynaphthalene (1.7 g).

Yield: 76 %
M.p. 241 - 243°C

Example 9

(a) 1-(N-Oxy-3-pyridyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene is treated in the same manner as in Example 8, and the resulting product is subjected to silica gel column chromatography (eluent; chloroform : methanol = 98 : 2).

From the fractions eluted first, there is obtained 1-(2(1H)-pyridon-3-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene.

(b) Further, from the fractions eluted later, there is obtained 1-(2(1H)-pyridon-5-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene.

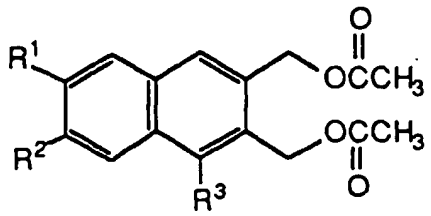
Example 10

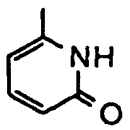
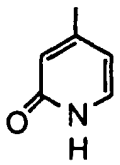
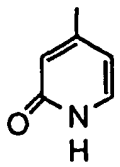
1-(N-Oxy-3-pyridyl)-2,3-bis(acetoxymethyl)-6,7-methylenedioxynaphthalene is treated in the same manner as in Example 9 to give 1-(2(1H)-pyridon-3-yl)-2,3-bis(acetoxymethyl)-6,7-methylenedioxynaphthalene and 1-(2(1 H)-pyridon-5-yl)-2,3-bis(acetoxymethyl)-6,7-methylenedioxynaphthalene.

Example 11

The corresponding N-oxypyridyl-type compounds are treated in the same manner as in Example 8 to give the compounds of Table 4.

Table 4



Ex. No.	R^1	R^2	R^3	Pysical properties
11-(1)	CH_3O	CH_3O		M.p. 238-240°C
11-(2)	CH_3CH_2O	CH_3O		M.p. 207-208°C
11-(3)	CH_3CH_2O	CH_3CH_2O		M.p. 213-214°C

Example 12

(a) 1-(2(1H)-Pyridon-4-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (1.9 g) is dissolved in dimethylformamide (20 ml), and thereto is added 63 % sodium hydride (0.17 g) under ice-cooling. The mixture is stirred at room temperature for 30 minutes, and cooled with ice. To the mixture is added methyl iodide (0.42 ml), and the mixture is stirred at room temperature overnight. The mixture is evaporated to remove the solvent, and to the residue are added ethyl acetate and water, and the mixture is separated. The organic layer is dried, and evaporated to give an oily product (1.0 g).

The resulting oily product is subjected to silica gel column chromatography (eluent; chloroform : acetone = 9 : 1, then, chloroform : methanol = 9 : 1). From the fractions eluted first, there is obtained 1-(2-methoxy-4-pyridyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene.

(b) From the fractions eluted later, there is obtained 1-(N-methyl-2(1H)-pyridon-4-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene.

Example 13

1-(N-Methyl-2(1H)-pyridon-4-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (0.5 g) is dissolved in a 10 % solution of ammonia in methanol (20 ml), and the mixture is allowed to stand at room temperature for 2 days. The mixture is evaporated to remove the solvent, and the resulting residue is purified by silica gel column chromatography (eluent; chloroform : methanol = 95 : 5) to give 1-(N-methyl-2(1H)-pyridon-4-yl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene (0.25 g).

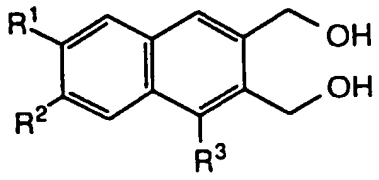
Yield: 63 %

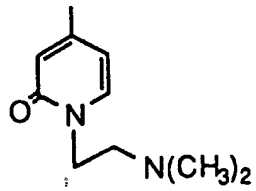
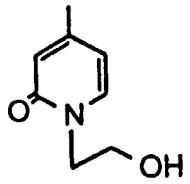
M.p. 176 - 178°C (recrystallized from ethanol)

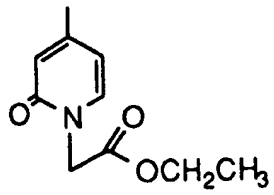
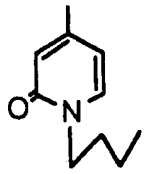
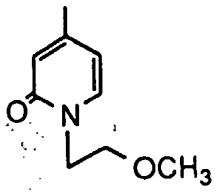
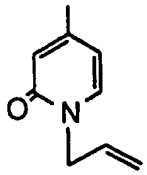
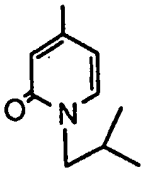
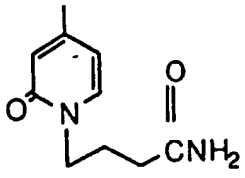
Example 14

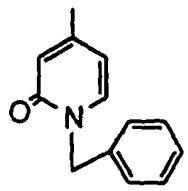
The corresponding pyridone-type compounds and the corresponding alkylating agent are treated in the same manner as in Example 12, and the obtained corresponding N-alkyl-pyridone-type compounds are further treated in the same manner as in Example 13 to give the compounds of Table 5.

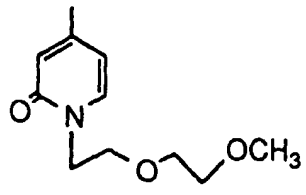
Table 5

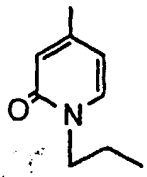


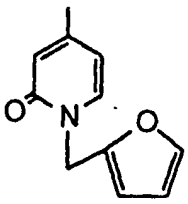
Ex. No.	R1	R2	R3	Physical properties
14-(1)	CH_3O	CH_3O		M.p. 140-142°C
14-(2)	CH_3O	CH_3O		M.p. 178-180°C

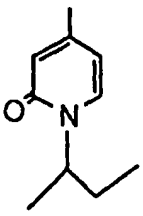
14-(3)	CH_3O	CH_3O		M.p. 158-160°C
14-(4)	CH_3O	CH_3O		M.p. 159-161°C
14-(5)	CH_3O	CH_3O		M.p. 124-126°C
14-(6)	CH_3O	CH_3O		M.p. 157-159°C
14-(7)	CH_3O	CH_3O		M.p. 188-189°C
14-(8)	CH_3O	CH_3O		M.p. 135-145°C

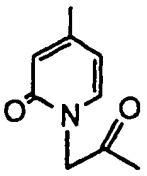
14-(9) CH_3O CH_3O  M.p. 226-227°C

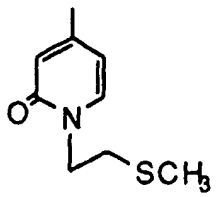
14-(10) CH_3O CH_3O  M.p. 125-126°C

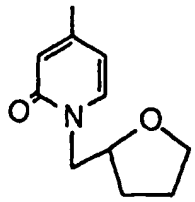
14-(11) CH_3O CH_3O  M.p. 193-194°C

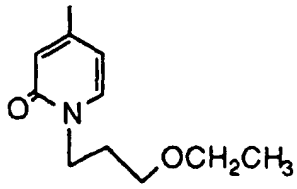
14-(12) CH_3O CH_3O  M.p. 195-196°C

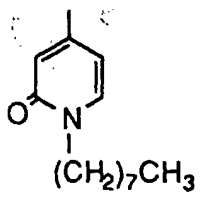
14-(13) CH_3O CH_3O  M.p. 136-137°C

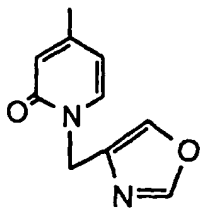
14-(14) CH_3O CH_3O  M.p. 100-102°C

14-(15) CH_3O CH_3O  M.p. 113-115°C

14-(16) CH_3O CH_3O  M.p. 185-187°C

14-(17) CH_3O CH_3O  M.p. 191-192°C

14-(18) CH_3O CH_3O  M.p. 110-112°C

14-(19) CH_3O CH_3O  M.p. 174-176°C

Example 15

(a) 1-(2(1H)-Pyridon-4-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene and ethyl bromoacetate are treated in the same manner as in Example 12 to give 1-(N-ethoxycarbonylmethyl-2(1H)-pyridon-4-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene.

(b) To a solution of the above product (2.0 g) in ethanol is added IN aqueous sodium hydroxide solution at room temperature, and the mixture is stirred for 3 hours. The mixture is evaporated to remove the ethanol, and to the residue is added water, and the mixture is washed with chloroform. The aqueous layer is collected, and the pH value thereof is adjusted with 10 % hydrochloric acid to pH 3, and the mixture is concentrated under reduced pressure to give 1-(N-carboxymethyl-2(1H)-pyridon-4-yl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene (1.2 g).

Yield: 64 %

M.p. >300°C

The above product is treated with an aqueous sodium hydrogen carbonate solution to give a sodium salt thereof.
Sodium salt: M.p. 170 - 195°C (decomposed)
Further, the above product is treated with conc. aqueous ammonia in methanol to give 1-(N-carbamoylmethyl-2(1H)-pyridon-4-yl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene as colorless needles.

M.p. 171 - 173°C (recrystallized from methanol)

Example 16

To a solution of 1-(2(1H)-pyridon-4-yl)-2,3-bis(acitoxymethyl)-6,7-dimethoxynaphthalene (1.0 g) and acrylonitrile (3 ml) in methanol is added sodium hydroxide (20 mg), and the mixture is heated at 80°C for 3 minutes. The reaction mixture is concentrated, and subjected to silica gel column chromatography (eluent; chloroform : acetone = 10 : 1, then 5 : 1), and from the desired fractions, there is obtained 1-[N-(2-cyanoethyl)-2(1H)-pyridon-4-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (1.1 g) as pale yellow oil.

Yield: 98 %

Example 17

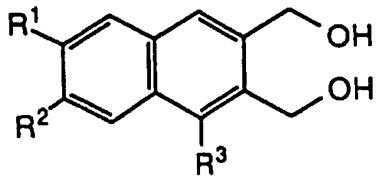
To a solution of 1-[N-(2-cyanoethyl)-2(1H)-pyridon-4-yl]-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (60 mg) in methanol is added sodium methylate (4 mg) at room temperature. The mixture is stirred for 30 minutes, and thereto is added acetic acid (4 mg), and the mixture is concentrated. The residue is purified by silica gel column chromatography (eluent; chloroform : methanol = 10 : 1) to give 1-[N-(2-cyanoethyl)-2(1H)-pyridon-4-yl]-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene (45 mg) as colorless crystal.

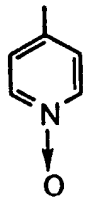
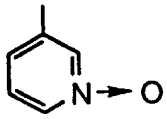
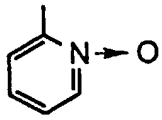
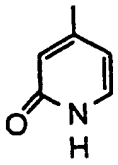
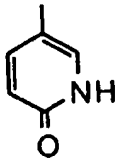
Yield: 91 %
M.p. 198 - 200°C

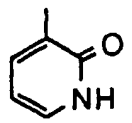
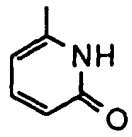
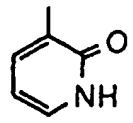
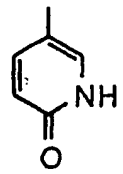
Example 18

The corresponding bis(acetoxymethyl)-type compounds are treated in the same manner as in Example 13 to give the compounds of Table 6.

Table 6



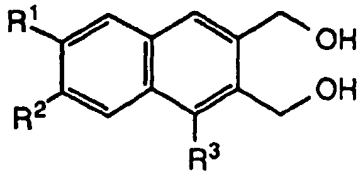
Ex. No.	R^1	R^2	R^3	Physical properties
18-(1)	CH_3O	CH_3O		M.p. 218-220°C
18-(2)	CH_3O	CH_3O		M.p. 153-155°C
18-(3)	CH_3O	CH_3O		M.p. 215-216°C
18-(4)	CH_3O	CH_3O		M.p. 242-244°C
18-(5)	CH_3O	CH_3O		M.p. 260-261°C

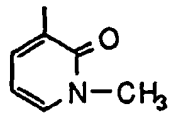
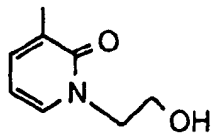
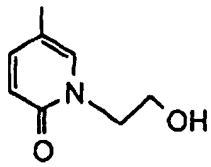
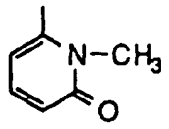
18-(6)	CH_3O	CH_3O		M.p. 248-250°C
18-(7)	CH_3O	CH_3O		M.p. 198-200°C
18-(8)		$-O-CH_2-O-$		M.p. >268°C
18-(9)		$-O-CH_2-O-$		M.p. 168-175°C

Example 19

The corresponding pyridone-type compounds are treated with the corresponding alkylating agent in the same manner as in Example 12, and the resulting N-alkylpyridone-type compounds are further treated in the same manner as in Example 13 to give the compounds of Table 7.

Table 7



Ex. No.	R1	R2	R3	Physical properties
19-(1)	CH_3O	CH_3O		M.p. 200-201°C
19-(2)	CH_3O	CH_3O		Oil
19-(3)	CH_3O	CH_3O		M.p. 123-125°C
19-(4)	CH_3O	CH_3O		M.p. 177-178°C

Example 20

(a) 1-(2(1H)-Pyridon-5-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene is treated with methyl iodide in the same manner as in Example 12. The resulting product is subjected to silica gel column chromatography (eluent; chloroform : acetone = 9 : 1, then chloroform : methanol = 9 : 1).
(b) From the fractions eluted first, there is obtained 1-(2-methoxy-5-pyridyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene. From the fractions eluted later, there is obtained 1-(N-methyl-2(1H)-pyridon-5-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene.

Example 21

1-(2-Methoxy-5-pyridyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene is treated in the same manner as in Example 13 to give 1-(2-methoxy-5-pyridyl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene.

M.p. 181 - 182°C

Example 22

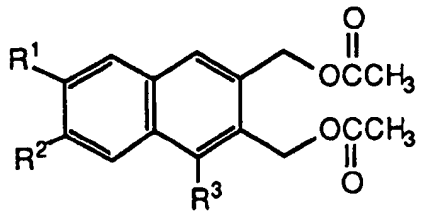
1-(N-Methyl-2(1H)-pyridon-5-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene is treated in the same manner as in Example 13 to give 1-(N-methyl-2(1H)-pyridon-5-yl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene.

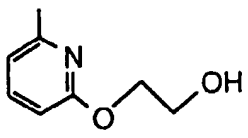
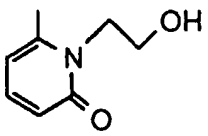
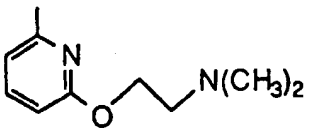
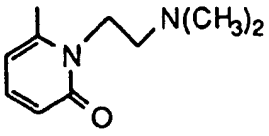
M.p. 212 - 214°C

Example 23

The corresponding pyridone-type compounds are treated with the corresponding alkylating agent in the same manner as in Example 20 to give the compound of Table 8.

Table 8



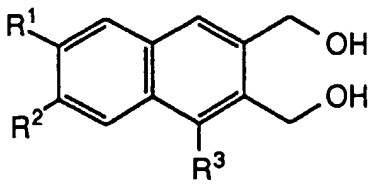
Ex. No.	R^1	R^2	R^3	Physical properties
23-(1)-(a)	CH_3O	CH_3O		Used in the next reaction without purification
23-(1)-(b)	CH_3O	CH_3O		Used in the next reaction without purification
23-(2)-(a)	CH_3O	CH_3O		Used in the next reaction without purification
23-(2)-(b)	CH_3O	CH_3O		Used in the next reaction without purification

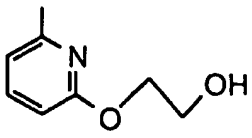
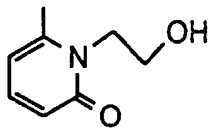
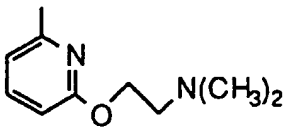
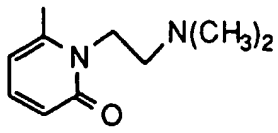
Example 24

The corresponding bis(acetoxymethyl)-type compounds are treated in the same manner as in Example 13 to give

the compounds of Table 9.

Table 9



Ex. No.	R^1	R^2	R^3	Physical properties
24-(1)	CH_3O	CH_3O		M.p. 156-158°C
24-(2)	CH_3O	CH_3O		M.p. 90-92°C
24-(3)	CH_3O	CH_3O		Oil
24-(4)	CH_3O	CH_3O		Oil

Example 25

To a solution of 1-(N-butyl-2(1H)-pyridon-4-yl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene (226 mg) in tetrahydrofuran (2 ml) is added sodium borohydride (100 mg), and the mixture is refluxed. To the reaction solution is added dropwise methanol (0.4 ml) over a period of time for 20 minutes. One hour thereafter, the reaction solution is allowed to cool, and neutralized with 10 % hydrochloric acid. The mixture is extracted with chloroform, and the chloroform layer is washed with water, dried and concentrated. The resulting residue is subjected to silica gel column chromatography (eluent; chloroform : methanol = 20 : 1), and the desired fractions are concentrated to give 1-(N-butyl-2(1 H)-pyridon-4-yl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene (165 mg) as crystal.

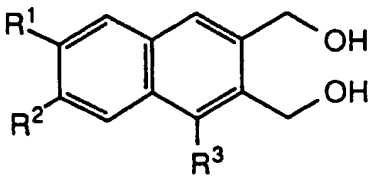
Yield: 83 %
M.p. 159 - 161°C

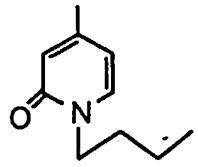
Example 26

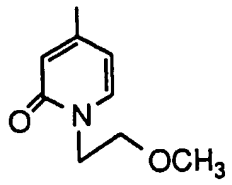
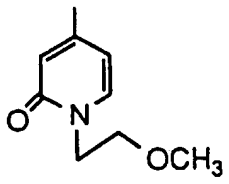
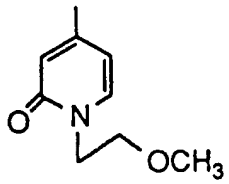
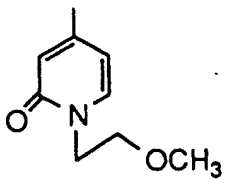
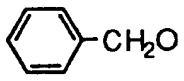
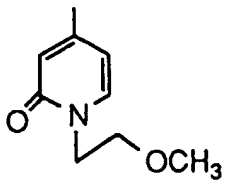
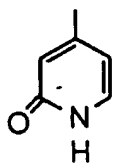
The corresponding dicarboxylic acid ester-type starting compounds are treated in the same manner as in Example

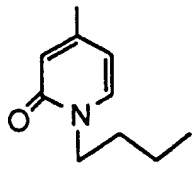
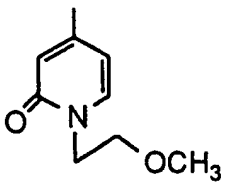
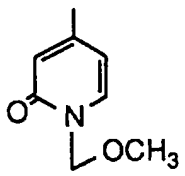
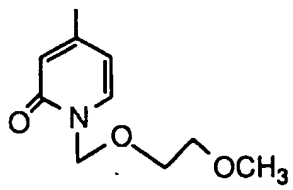
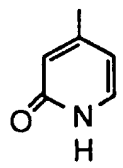
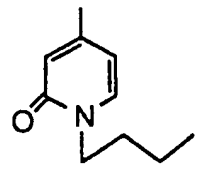
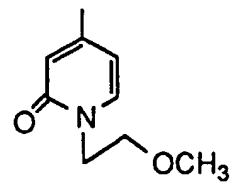
25 to give the compounds of Table 10.

Table 10

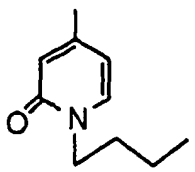


Ex. No.	R1	R2	R3	Phycical properties
26-(1)	CH_3O	CH_3CH_2O		M.p. 164 - 166°C

26-(2)	CH_3O	CH_3CH_2O		M.p. 168 - 170°C
26-(3)	CH_3O	$HOCH_2CH_2O$		M.p. 154 - 155°c
26-(4)	CH_3O	CH_3O-CH_2CH_2O		M.p. 170 - 172°C
26-(5)	CH_3O	CH_3OCH_2 - CH_2OCH_2O		M.P. 108 - 109°C
26-(6)	CH_3O			M.p. 143 - 144°C
26-(7)	CH_3CH_2O	CH_3O		M.p. 158 - 159°C

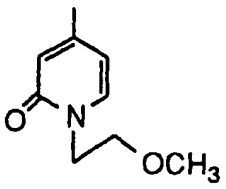
26-(8)	CH_3CH_2O	CH_3O		M.p. 173 - 175°C
26-(9)	CH_3CH_2O	CH_3O		M.p. 162 - 164°C
26-(10)	CH_3CH_2O	CH_3O		M.p. 159 - 160°C
26-(11)	CH_3CH_2O	CH_3O		M.p. 93 - 94°C
26-(12)	CH_3CH_2O	CH_3CH_2O		M.p. 247 - 248°C
26-(13)	CH_3CH_2O	CH_3CH_2O		M.p. 149 - 150°C
26-(14)	CH_3CH_2O	CH_3CH_2O		M.p. 126 - 127°C

26-(15) $HOCH_2CH_2O$ CH_3O



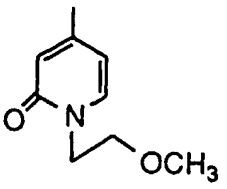
M.p. 162 - 164°C

26-(16) $HOCH_2CH_2O$ CH_3O



M.p. 169 - 171°C

26-(17) $HOCH_2CH_2O$ CH_3O



M.p. 133 - 135°C

Example 27

(a) To a suspension of 1-(4-pyridyl)-2,3-bis(hydroxymethyl)-6,7-diethoxynaphthalene (7.0 g) in dry dimethylformamide (14 ml) is added 2-methoxyethyl iodide (7.35 g), and the mixture is stirred at 80°C overnight. The mixture is allowed to cool, and thereto added ethyl acetate. The precipitated crystal is collected by filtration to give 4-[2,3-bis (hydroxymethyl)-6,7-diethoxy-1-naphthyl]-N-(2-methoxyethyl)pyridinium iodide (8.50 g).

Yield: 79.8 %
M.p. 174 - 176°C (recrystallized from acetone)

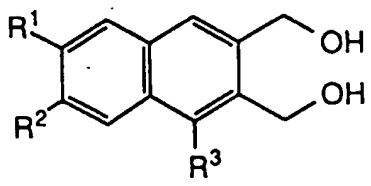
(b) To a mixture of the above product (2.0 g) in water (5 ml) and methanol (10 ml) are simultaneously added dropwise a solution of potassium ferricyanide (4.8 g) in water (10 ml) and 2N aqueous sodium hydroxide solution (15.2 ml) with stirring at 10°C over a period of time for one hour. The mixture is warmed to room temperature, and stirred for 5 hours. The mixture is evaporated to remove the methanol, and the residue is extracted with methylene chloride. The extract is washed, dried, and concentrated. The resulting residue is crystallized from ethyl acetate to give 1-[N-(2-methoxyethyl)-2(1H)-pyridon-4-yl]-2,3-bis(hydroxymethyl)-6,7-diethoxynaphthalene (1.82 g).

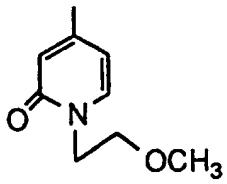
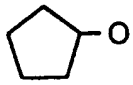
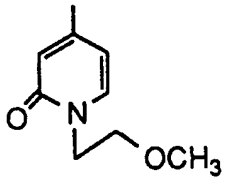
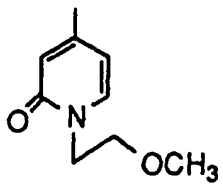
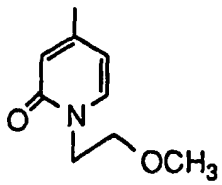
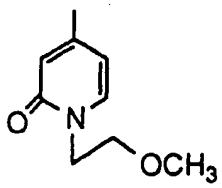
Yield: 60.1 %
M.p. 126 - 127°C

Example 28

The corresponding compounds are treated in the same manner as in Example 27 to give the compounds of Table 11.

Table 11



Ex. No.	R1	R2	R3	Physical properties
28-(1)	CH_3O	$(CH_3)_2CHO$		M.p. 184 - 185°C
28-(2)	CH_3O			M.p. 216 - 217°C
28-(3)	CH_3CH_2O	CH_3O		M.p. 162 - 164°C
28-(4)	CH_3CH_2O	$CH_3(CH_2)_2O$		M.p. 119 - 121°C
28-(5)	CH_3CH_2O	$CH_3(CH_2)_4O$		M.p. 118 - 120°C

Example 29

To a solution of 1-(1-oxo-3-ethoxycarbonylpropyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (340 mg) in ethanol (40 ml) is added hydrazine hydrate (1 ml), and the mixture is refluxed overnight. The reaction solution is allowed to cool, and concentrated. To the resulting residue is added water, and the mixture is extracted with chloroform. The chloroform layer is washed with water, dried, and concentrated to give 1-(4,5-dihydro-3(2H)-pyridazinon-6-yl)-2,3-bis (hydroxymethyl)-6,7-dimethoxynaphthalene (170 mg) as crystal.

Yield: 67 %
M.p. 210 - 212°C

Example 30

(a) To a solution of 1-(4,5-dihydro-3(2H)-pyridazinon-6-yl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene (344 mg) in methylene chloride (10 ml) are added triethylamine (1.24 ml) and dimethylaminopyridine (20 mg). To the mixture is added acetic anhydride (896 mg) at room temperature, and the mixture is stirred for 4 days. The reaction solution is washed with water, dried over magnesium sulfate and concentrated. The resulting residue is purified by silica gel column chromatography (eluent; chloroform : acetone = 5 : 1). The desired fractions are concentrated, and the residue is crystallized from diethyl ether to give 1-(4,5-dihydro-3(2H)-pyridazinon-6-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (255 mg).

Yield: 60 %
M.p. 184 - 186°C

(b) To a solution of the above product (200 mg) in dioxane (5 ml) is added dicyanodichloroquinone (427 mg), and the mixture is refluxed for 2 hours. The mixture is allowed to cool, and concentrated, and chloroform is added to the resulting residue. The insoluble materials are removed by filtration, and the filtrate is washed with water, dried, and concentrated. The resulting residue is purified by silica gel column chromatography (eluent; chloroform : acetone = 5 : 1), and the desired fractions are concentrated to give 1-(3(2H)-pyridazinon-6-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (150 mg) as an oily product.

Yield: 75 %

(c) To a solution of the above product (100 mg) in methanol (5 ml) is added sodium methylate (30 mg) at room temperature. After stirring for one hour, to the mixture is added acetic acid (34 mg), and the mixture is concentrated. The residue is purified by silica gel column chromatography (eluent; chloroform : methanol = 10 : 1), and the desired fractions are concentrated. The residue is crystallized from diethyl ether to give 1-(3(2H)-pyridazinon-6-yl)-2,3-bis (hydroxymethyl)-6,7-dimethoxynaphthalene (40 mg).

Yield: 51 %
M.p. 228 - 229°C

Example 31

To a solution of 1-(N-butyl-2(1H)-pyridon-4-yl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene (1.5 g) in methylene chloride (10 ml) are added successively triethylamine (1.3 ml), dimethylaminopyridine (300 mg) and acetic anhydride (853 mg) at room temperature. After stirring at room temperature overnight, the reaction solution is washed with water, and the methylene chloride layer is dried and concentrated. The residue is purified by silica gel column chromatography (eluent; chloroform : methanol = 20 : 1), and the desired fractions are concentrated. The precipitated crystal is collected by filtration to give 1-(N-butyl-2(1H)-pyridon-4-yl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (1.40 g).

Yield: 77 %
M.p. 134 - 135°C

Example 32

To a suspension of 1-[N-(2-methoxyethyl)-2(1H)pyridon-4-yl]-2,3-bis(hydroxymethyl)-6-ethoxy-7-methoxynaph-

thalene in pyridine is added pivaloyl chloride (2.86 ml) under ice-cooling. The mixture is warmed to room temperature, and stirred overnight. The mixture is evaporated to remove the pyridine, and to the residue are added water and ethyl acetate, and separated. The ethyl acetate layer is washed, dried, and concentrated, and the resulting residue is subjected to silica gel column chromatography (eluent; chloroform : acetone = 5 : 1, then chloroform : methanol = 20 : 1). The desired fractions are concentrated, and the resulting residue is crystallized from diethyl ether to give 1-[N-(2-methoxyethyl)-2(1H)-pyridon-4-yl]-2-hydroxymethyl-3-pivaloyloxymethyl-6-ethoxy-7-methoxynaphthalene (5.3 g).

Yield: 55 %
M.p. 134 - 135°C

Example 33

To a suspension of sodium hydride in hexamethylphosphoric triamide (40 ml) is added a solution of 1-(3-pyridyl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene in hexamethylphosphoramide (10 ml) under ice-cooling. The mixture is warmed to room temperature, and then stirred for 30 minutes. To the reaction solution is added neo-pentyl tosylate (3.67 g), and the mixture is reacted at 100°C for 30 minutes. The mixture is allowed to cool, and thereto is added water, and the mixture is extracted with ethyl acetate. The extract is washed with water, dried, and concentrated. The resulting residue is subjected to silica gel column chromatography (eluent; chloroform : acetone = 5 : 1), and the desired fractions are concentrated to give 1-(3-pyridyl)-2-hydroxymethyl-3-neo-pentyloxymethyl-6,7-dimethoxynaphthalene (1.5 g) as an oily product.

A solution of the above product in chloroform is treated with a solution of hydrogen chloride in methanol to give a hydrochloride of the above product.

Hydrochloride: M.p. 135 - 145°C (recrystallized from diethyl ether)

Reference Example 1

(a) 3,4-Dimethoxybenzaldehyde (398.8 g) is dissolved in acetic acid (1.8 liter), and thereto is added dropwise bromine (136 ml) at room temperature over a period of time for 4 hours. After stirring overnight, to the mixture is added dropwise bromine (60 ml) gradually, and the mixture is stirred overnight. To the reaction solution is added water (7 liters), and the precipitated crystal is collected by filtration, washed with water to give a crystalline product, which is dissolved in chloroform (2 liters). The mixture is washed successively with water, aqueous sodium thiosulfate solution and a saturated sodium chloride solution. The chloroform layer is dried and concentrated, and crystallized from diisopropyl ether to give 6-bromo-3,4-dimethoxygbenzaldehyde (470 g) as colorless crystal.

Yield: 79.9 %
M.p. 144 - 146°C

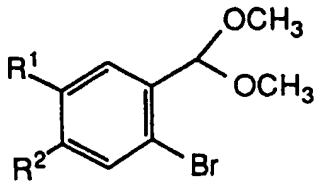
(b) 6-Bromo-3,4-dimethoxybenzaldehyde (470 g) is suspended in methanol (600 ml), and thereto are added methyl ortho-formate (1025 ml) and IRA-120 (H^+-type) (10 g), and the mixture is refluxed for one hour. The mixture is cooled to room temperature, and the insoluble materials are removed by filtration. The filtrate is concentrated under reduced pressure, and the resulting residue is dissolved in diethyl ether. The mixture is washed, dried, and evaporated to remove the diethyl ether. The resulting residue is distilled under reduced pressure to give 6-bromo-3,4-dimethoxybenzaldehyde dimethylacetal (522 g) as main distillate (133-138°C/1 Torr).

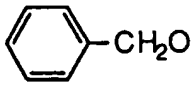
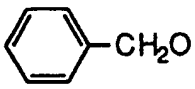
Yield: 93.9 %

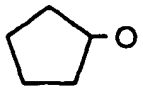
Reference Example 2

The corresponding aldehyde-type starting compounds are treated in the same manner as in Reference Example 1 to give the compounds of Table 12.

Table 12



Ref. Ex. No.	R^1	R^2	Physical properties
2-(1)	H	H	Oil
2-(2)	CH_3O	CH_3O	b.p. 133-138°C/1 Torr
2-(3)	CH_3CH_2O	CH_3O	b.p. 170-175°C/3 Torr
2-(4)	CH_3O	CH_3CH_2O	b.p. 160-162°C/2 Torr
2-(5)	-O-CH_2-O-		Oil
2-(6)	CH_3CH_2O	CH_3CH_2O	b.p. 145-150°C/1 Torr
2-(7)	CH_3O		Oil
2-(8)		CH_3O	Oil
2-(9)	CH_3CH_2O	$CH_3(CH_2)_2O$	Oil
2-(10)	CH_3CH_2O	$CH_3(CH_2)_4O$	Oil

2-(11) CH_3O  b.p. 150-155°C/1 Torr

Reference Example 3

A solution of 6-bromo-3,4-dimethoxybenzaldehyde dimethylacetal compound (20 g) in tetrahydrofuran (100 ml) is cooled to -60°C, and thereto is added dropwise a solution of n-butyl lithium in hexane (1.6M, 45.1 ml) over a period of time for 20 minutes under nitrogen atmosphere. The reaction solution is reacted at the same temperature for 30 minutes, and thereto is added dropwise a solution of isonicotinic aldehyde (7.36 g) in tetrahydrofuran (50 ml) over a period of time for 20 minutes. After reacting for one hour, to the reaction solution are added water and ethyl acetate (200 ml), and the mixture is separated. The ethyl acetate layer is washed with a saturated sodium chloride solution, dried over magnesium sulfate, and evaporated to remove the ethyl acetate to give 3,4-dimethoxy-6-(4-pyridyl)-hydroxymethyl-benzaldehyde dimethylacetal (15.4 g).

Yield: 70 %
M.p. 120 - 125°C

Reference Example 4

The corresponding compounds are treated in the same manner as in Reference Example 3 to give the compounds of Table 13.

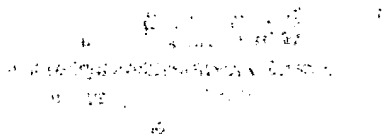
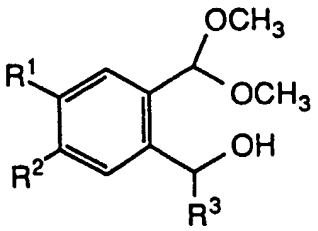
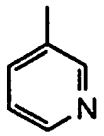
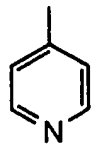
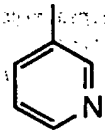
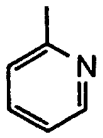
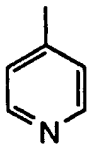
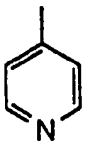
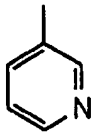
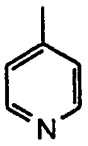
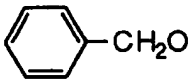
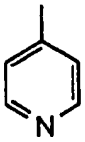
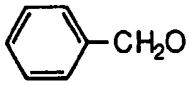
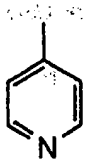
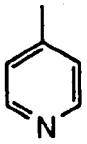
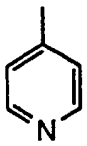
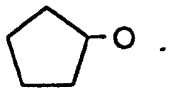
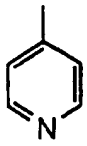


Table 13



Ref. Ex. No.	R^1	R^2	R^3	Physical properties
4-(1)	H	H		Oil
4-(2)	CH_3O	CH_3O		Oil
4-(3)	CH_3O	CH_3O		Oil
4-(4)	CH_3O	CH_3O		Oil
4-(5)	CH_3O	CH_3O	CH_3	Oil
4-(6)	CH_3CH_2O	CH_3O		M.p. 114-115°C

4-(7)	CH_3O	CH_3CH_2O		M.p. 116-118°C
4-(8)	-O-CH_2-O-			Oil
4-(9)	CH_3CH_2O	CH_3CH_2O		M.p. 108-109°C
4-(10)	CH_3O			Oil
4-(11)		CH_3O		Oil
4-(12)	CH_3CH_2O	$CH_3(CH_2)_2O$		M.p. 110-112°C
4-(13)	CH_3CH_2O	$CH_3(CH_2)_4O$		M.p. 106-109°C
4-(14)	CH_3O			Oil

Reference Example 5

3,4-Dimethoxy-6-(4-pyridyl)hydroxymethylbenzaldehyde dimethylacetal (15 g) is refluxed for 3 hours in a mixture of methanol (200 ml) and acetic acid (30 ml). The mixture is evaporated to about 1/4 volume, and separated with a

mixture of chloroform and aqueous sodium hydrogen carbonate solution. The organic layer is collected, dried, and concentrated to give 1-methoxy-3-(4-pyridyl)-5,6-dinethoxyphthalene (13.1 g) as an oil, which is used in the subsequent reaction without purification.

Yield: 94 %

Reference Example 6

To a solution of lithium diisopropylamide (18.4 g) in tetrahydrofuran (300 ml) is added dropwise a solution of 1-methoxy-3-(4-pyridyl)-5,6-dimethoxyphthalene (13.1 g) in tetrahydrofuran (100 ml) at -70°C, and the mixture is stirred. To the mixture are successively added dropwise acetic acid (10.9 g) and dimethyl maleate (13.1 g), and the mixture is stirred at room temperature overnight. The reaction mixture is separated with ethyl acetate and aqueous sodium hydrogen carbonate solution. The organic layer is collected, washed with water, dried, and concentrated. The residue is subjected to silica gel column chromatography (eluent; n-hexane : ethyl acetate = 1 : 1) to give 1-(4-pyridyl)-2,3-bis (methoxycarbonyl)-6,7-dimethoxy-1,4-epoxy-1,4-dihydronaphthalene (3.5 g).

Reference Example 7

1-(4-Pyridyl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxy-1,4-epoxy-1,4-dihydronaphthalene (3.0 g) and trifluoroborane·diethyl ether (1.95 g) are added to acetonitrile (100 ml), and the mixture is refluxed for 2 hours. The reaction solution is separated with a mixture of chloroform (300 ml) and aqueous sodium hydrogen carbonate solution (50 ml), and the organic layer is further washed with aqueous sodium hydrogen carbonate solution, dried, and concentrated. The resulting residue is washed with a small amount of diethyl ether to give 1-(4-pyridyl)-2,3-bis(methoxy-carbonyl)-6,7-dimethoxynaphthalene (2.1 g) as crystal.

Yield: 73 %
M.p. 196 - 198°C

Reference Example 8

To a solution of 3,4-dimethoxy-6-(4-pyridyl)hydroxymethylbenzaldehyde dimethylacetai (18.4 g) in a mixture of acetic acid (50 ml) and toluene (50 ml) is added dimethyl maleate (8.64 ml), and the mixture is refluxed for one hour. To the mixture is added methanesulfonic acid (9.33 ml), and the mixture is refluxed for 8 hours while removing the resulting water with a Dean-Stalk apparatus. The mixture is cooled to room temperature, and concentrated. The residue is dissolved in chloroform, and the pH value thereof is adjusted with aqueous potassium carbonate solution to pH 8. The mixture is extracted twice with each 100 ml of chloroform, and the extracts are washed with a saturated sodium chloride solution, dried over magnesium sulfate, and concentrated. The resulting residue is crystallized from diethyl ether to give a diester compound, 1-(4-pyridyl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene (13.5 g).

Yield: 62.2 %
M.p. 196 - 198°C

Reference Example 9

1-(4-Pyridyl)-2,3-bis(methoxycarbonyl)-6-benzyloxy-7-methoxynaphthalene (2.3 g) is dissolved in acetic acid (50 ml), and thereto is added 10 % palladium-carbon. The mixture is subjected to hydrogenation for 3 hours with shaking by using a moderate-pressure reduction apparatus (Parr). The palladium-carbon is removed by filtration, and the filtrate is concentrated. The precipitated crystal is washed with diethyl ether to give 1-(4-pyridyl)-2,3-bis(methoxycarbonyl)-6-hydroxy-7-methoxynaphthalene (1.8 g).

Yield: 98 %
M.p. 210 - 212°C

Reference Example 10

To a solution of 1-(4-pyridyl)-2,3-bis(methoxycarbonyl)-6-hydroxy-7-methoxynaphthalene (17 g) in dimethylformamide (50 ml) is added gradually sodium hydride (60 % dispersion-type) under ice-cooling, and the mixture is stirred at room temperature for 30 minutes. The mixture is cooled with ice, and thereto is added 2-methoxyethyl iodide (10.3 g).

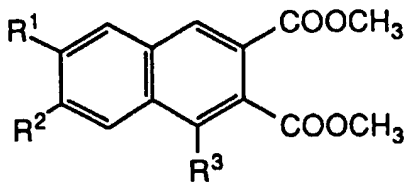
The mixture is stirred at room temperature for 2 hours, and heated to 80°C. One hour thereafter, the reaction solution is allowed to cool, and concentrated. The resulting residue is dissolved in ethyl acetate, washed with water, dried, and concentrated. The precipitated crystal is washed with diethyl ether to give 1-(4-pyridyl)-2,3-bis(methoxycarbonyl)-6-(2-methoxyethyloxy)-7-methoxynaphthalene (8.5 g).

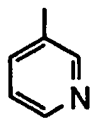
Yield: 43 %
M.p. 156 - 158°C

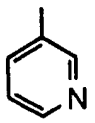
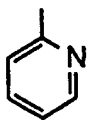
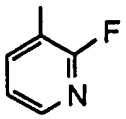
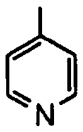
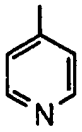
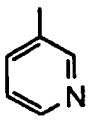
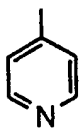
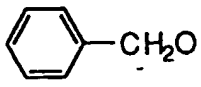
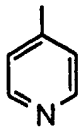
Reference Example 11

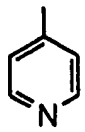
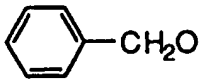
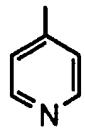
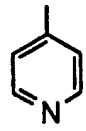
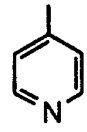
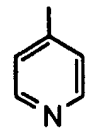
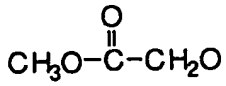
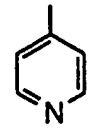
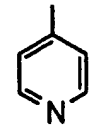
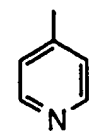
The corresponding compounds are treated in the same manner as in Reference Examples 1 to 8, and the obtained products are further treated in the same manner as in Reference Examples 9, 10, if necessary, to give the dicarboxylic acid ester-type compounds of Table 14.

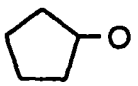
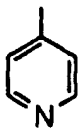
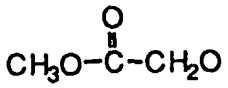
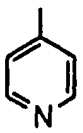
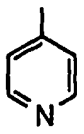
Table 14



Ref. Ex. No.	R^1	R^2	R^3	Physical properties
11-(1)	H	H		Oil

11-(2)	CH_3O	CH_3O		Oil
11-(3)	CH_3O	CH_3O		M.p. 163 - 165°C
11-(4)	CH_3O	CH_3O	CH_3	M.p. 142 - 144°C
11-(5)	CH_3O	CH_3O		Powder
11-(6)	CH_3CH_2O	CH_3O		M.p. 186 - 187°C
11-(7)	CH_3O	CH_3CH_2O		M.p. 179 - 181°C
11-(8)	-O-CH_2-O-			M.p. 156 - 157°C
11-(9)	CH_3CH_2O	CH_3CH_2O		M.p. 149 - 150°C
11-(10)	CH_3O			M.p. 202 - 203°C

11-(11)	CH_3O	HO		M.p. 261 - 262°C
11-(12)		CH_3O		M.p. 236 - 238°C
11-(13)	HO	CH_3O		M.p. 210 - 212°C
11-(14)	CH_3CH_2O	$CH_3(CH_2)_2O$		M.p. 159 - 161°C
11-(15)	CH_3CH_2O	$CH_3(CH_2)_4O$		M.p. 147 - 149°C
11-(16)	CH_3O			M.p. 176 - 178°C
11-(17)	CH_3O	$CH_3OCH_2CH_2O$		M.p. 156 - 157°C
11-(18)	CH_3O	$CH_3OCH_2CH_2OCH_2O$		M.p. 90-92°C

11-(19)	CH_3O				M.p. 150 - 152°C
11-(20)		CH_3O			M.p. 214 - 215°C
11-(21)	$CH_3OCH_2CH_2O$	CH_3O			M.p. 156 - 158°C

Reference Example 12

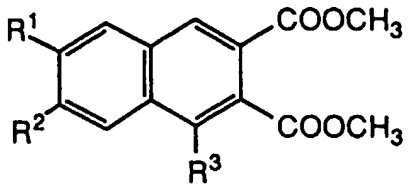
To a solution of 1-(4-pyridyl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene (5 g) in methylene chloride (300 ml) is added m-chloroperbenzoic acid (8.1 g) under ice-cooling, and the mixture is warmed to room temperature, and stirred overnight. The reaction solution is washed successively with 10 % aqueous sodium hydrogensulfite solution, aqueous potassium carbonate solution and saturated sodium chloride solution. The mixture is dried, and concentrated to give 1-(N-oxy-4-pyridyl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene (15.0 g) as crystal.

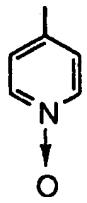
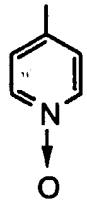
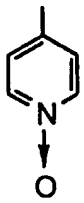
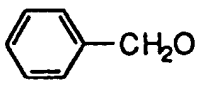
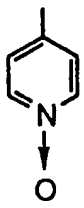
Yield: 96 %
M.p. 224 - 226°C

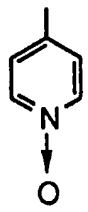
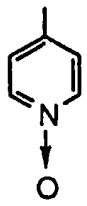
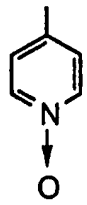
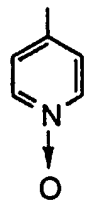
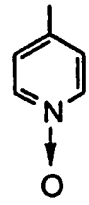
Reference Example 13

The corresponding pyridine-type starting compounds are treated in the same manner as in Reference Example 12 to give the compounds of Table 15.

Table 15



Ref. Ex. No.	R1	R2	R3	Physical properties
13-(1)	CH_3CH_2O	CH_3O		M.p. 190 - 197°C
13-(2)	CH_3O	CH_3CH_2O		M.p. 220 - 230°C
13-(3)	CH_3CH_2O	CH_3CH_2O		M.p. 177 - 178°C
13-(4)	CH_3O			Used in the next reaction without purifiifcation

13-(5)	CH_3O	$CH_3OCH_2CH_2O$		M.p. 188 - 189°C
13-(6)	CH_3O	$CH_3O-\overset{O}{\overset{\|\|}{C}}-CH_2O$		Used in the next reaction without purification
13-(7)	$CH_3O-\overset{O}{\overset{\|\|}{C}}-CH_2O$	CH_3O		M.p. 227 - 228°C
13-(8)	$CH_3OCH_2CH_2O$	CH_3O		M.p. 161 - 163°C
13-(9)	CH_3O	$CH_3OCH_2CH_2-OC_2H_5$		———

Reference Example 14

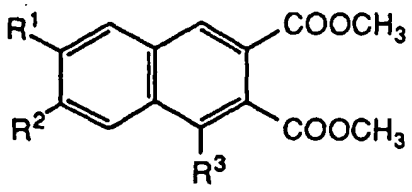
To a solution of 1-(N-oxy-4-pyridyl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene (10 g) in dimethylformamide (75 ml) ia added acetic anhydride (24 ml), and the mixture is stirred at 150°C for 8 hours. The reaction solution is allowed to cool, and concentrated. The resulting residue is dissolved in methanol (20 ml), and thereto is added saturated aqueous ammonia (10 ml) at room temperature, and the mixture is stirred for 30 minutes. The precipitated crystal is collected by filtration to give 1-(2(1H)-pyridon-4-yl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene (8.6 g).

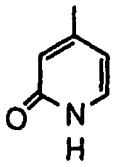
Yield: 86 %
M.p. >250°C

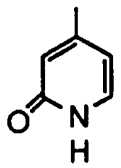
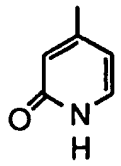
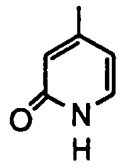
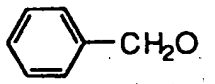
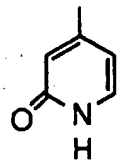
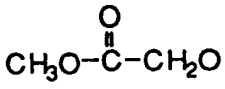
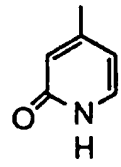
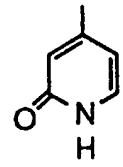
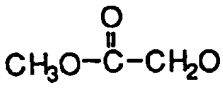
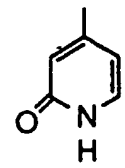
Reference Example 15

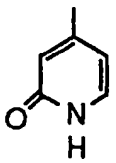
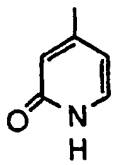
The corresponding N-oxypyridine-type starting compounds are treated in the same manner as in Reference Example 14 to give the pyridone-type compounds of Table 16.

Table 16



Ref. Ex. No.	R^1	R^2	R^3	Physical properties
16-(1)	CH_3O	CH_3O		M.p. >250°C

16-(2)	CH_3CH_2O	CH_3O		M.p. >235°C
16-(3)	CH_3O	CH_3CH_2O		M.p. 225 - 228°C
16-(4)	CH_3CH_2O	CH_3CH_2O		M.p. 234 - 235°C
16-(5)	CH_3O			M.p. 251 - 252°C
16-(6)	CH_3O			M.p. 148 - 149°C
16-(7)	CH_3O	$CH_3OCH_2CH_2O$		Oil
16-(8)		CH_3O		M.p. 225 - 228°C

16-(9)	$CH_3OCH_2CH_2O$	CH_3O		M.p. 207 - 206°C
16-(10)	CH_3O	$CH_3OCH_2CH_2$-OCH_2O		Used in the next reaction without purification

Reference Example 16

To a solution of 1-(2(1H)-pyridon-4-yl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene (4.0 g) in dimethylformamide (15 ml) is added sodium hydride (60 % dispersion-type) (404 mg) under ice-cooling, and the mixture is warmed to room temperature. The reaction mixture is stirred for 30 minutes, and cooled again with ice. To the reaction solution is added n-butyl iodide (2.2 g), and the mixture is warmed to room temperature and stirred overnight. The reaction solution is concentrated, and the resulting residue is dissolved in ethyl acetate, and washed with water. The mixture is dried and concentrated, and the resulting residue is subjected to silica gel column chromatography (eluent; hexane : ethyl acetate = 3 : 1), and the desired fractions are concentrated to give 1-(N-butyl-2(1H)-pyridon-4-yl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene (2.5 g) as crystal.

Yield: 55 %
M.p. 144 - 146°C

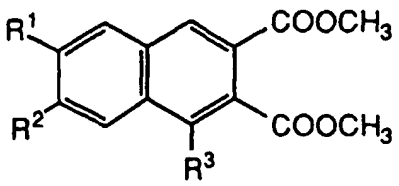
As a side product, there is obtained 1-(2-butoxy-4-pyridyl)-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene (1.4 g).

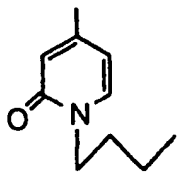
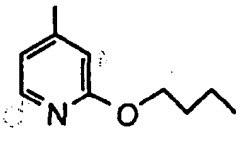
Yield: 31 %
M.p. 112 - 113°C (crystallized from ethanol)

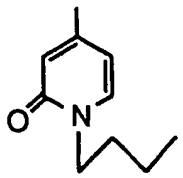
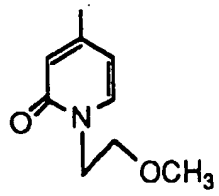
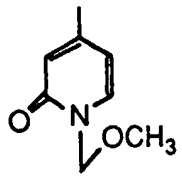
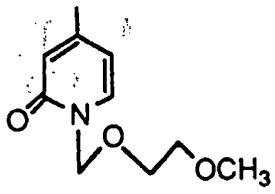
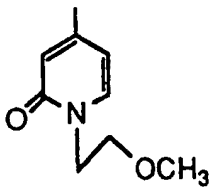
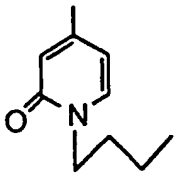
Reference Example 17

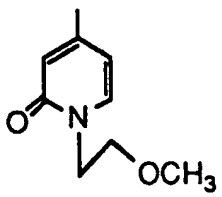
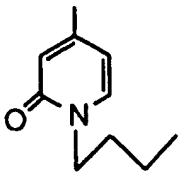
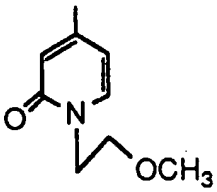
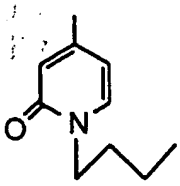
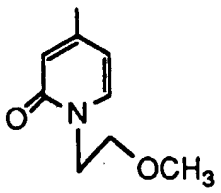
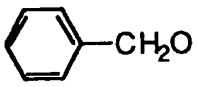
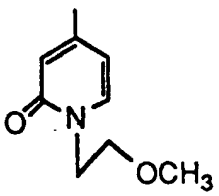
The corresponding pyridone-type starting compounds are treated in the same manner as in Reference Example 16 to give the compounds of Table 17.

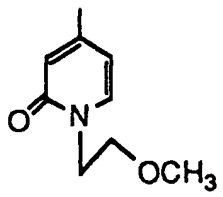
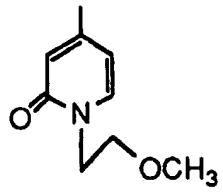
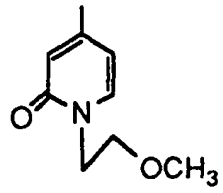
Table 17



Ref. Ex. No.	R^1	R^2	R^3	Physical properties
17-(1)	CH_3O	CH_3O		M.p. 144 - 146°C
17-(2)	CH_3O	CH_3O		M.p. 112 - 113°C

17-(3)	CH_3CH_2O	CH_3O		M.p. 129 - 131°C
17-(4)	CH_3CH_2O	CH_3O		M.p. 147 - 149°C
17-(5)	CH_3CH_2O	CH_3O		M.p. 124 - 125°C
17-(6)	CH_3CH_2O	CH_3O		Oil
17-(7)	CH_3CH_2O	CH_3CH_2O		M.p. 103 - 104°C
17-(8)	CH_3CH_2O	CH_3CH_2O		M.p. 98 - 99°C

17-(9)	$CH_3O-\overset{O}{\overset{\|}{C}}-CH_2O$	CH_3O		M.p. 171 - 173°C
17-(10)	$CH_3O-\overset{O}{\overset{\|}{C}}-CH_2O$	CH_3O		M.p. 120 - 122°C
17-(11)	$CH_3OCH_2CH_2O$	CH_3O		M.p. 124 - 126°C
17-(12)	CH_3O	CH_3CH_2O		M.p. 131 - 132°C
17-(13)	CH_3O	CH_3CH_2O		M.p. 167 - 168°C
17-(14)	CH_3O			Oil

17-(15)	CH_3O	$CH_3O-\overset{O}{\overset{\|}{C}}-CH_2O$		Oil
17-(16)	CH_3O	$CH_3OCH_2CH_2O$		Oil
17-(17)	CH_3O	CH_3OCH_2 - CH_2OCH_2O		Oil

Reference Example 18

(a) 6-Bromo-3,4-dimethoxybenzaldehyde dimethylacetal and acetaldehyde are treated in the same manner as in Reference Example 3 to give 3,4-dimethoxy-6-(1-hydroxyethyl)-benzaldehyde dimethylacetal as oil.
(b) The above product is treated in the same manner as in Reference Example 8 to give 1-methyl-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene.

M.p. 142 - 144°C

(c) 1-Methyl-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene is treated in the same manner as in Example 1 to give 1-methyl-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene.

M.p. 180 - 182°C

(d) The above product is treated in the same manner as in Example 4 to give 1-methyl-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene.

M.p. 130 - 131°C

(e) To a solution of 1-methyl-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (5.0 g) in carbon tetrachloride (100 ml) are added N-bromosuccinimide (2.8 g) and benzoyl peroxide (150 mg), and the mixture is refluxed for 2 hours. The mixture is allowed to cool, and the insoluble materials are separated by filtration, and the filtrate is concentrated under reduced pressure to give 1-bromomethyl-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (5.1 g) as crystal.

Yield: 83 %
M.p. 182 - 183°C

(f) To a solution of the above product (4.0 g) in chloroform (70 ml) is added tetrabutylammonium dichromate (8.8 g), and the mixture is refluxed for 2 hours. The mixture is allowed to cool, and then concentrated. The resulting

residue is purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate = 2 : 1), and the fractions containing the desired compound are concentrated to give 1-formyl-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (1.4 g) as crystal.

Yield: 41 %
M.p. 154 - 155°C

(g) To a solution of the above product (5.0 g) in methylene chloride (30 ml) are added dropwise titanium chloride (1.7 ml) and 1-ethoxy-1-trimethylsilyloxycyclopropane (2.9 g) at -70°C under nitrogen atmosphere. The reaction solution is gradually warmed, and stirred at 0°C for one hour, and then thereto is added a saturated sodium chloride solution. The mixture is extracted with chloroform, and the chloroform layer is washed with water, and dried over magnesium sulfate. The mixture is concentrated, and the resulting residue is purified by silica gel column chromatography (eluent; hexane : chloroform : ethyl acetate = 5 : 5 : 2, then hexane : ethyl acetate = 1 : 1) to give 1-(1-hydroxy-3-ethoxycarbonylpropyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (4.0 g) as oil.

Yield: 62 %

(h) To a suspension of pyridium chlorochromate (794 mg) in methylene chloride (10 ml) is added dropwise a solution of the above product (462 mg) in methylene chloride (5 ml) under ice-cooling. The mixture is warmed to room temperature, and reacted for three hours. To the mixture is added diethyl ether, and the mixture is separated by decantation. The resulting residue is subjected twice to decantation with diethyl ether, and further subjected twice to decantation with chloroform. The organic layers are combined, and filtered. The filtrate is concentrated, and the resulting residue is purified by silica gel column chromatography (eluent; hexane : chloroform : ethyl acetate = 5 : 5 : 2). The desired fractions are concentrated to give 1-(1-oxo-3-ethoxycarbonylpropyl)-2,3-bis(acetoxymethyl)-6,7-dimethoxynaphthalene (400 mg) as crystal.

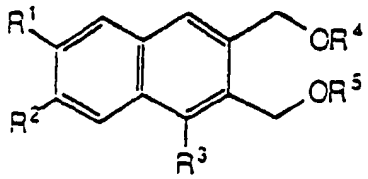
Yield: 87 %
M.p. 85 - 87°C

The desired compounds [I] of the present invention and pharmaceutically acceptable salts thereof have excellent bronchodilating activity, and are useful as medicines in the prophylaxis and treatment of asthma. That is, the desired compounds [I] of the present invention can effectively inhibit bronchoconstriction induced by various spasmogen or antigen such as histamine, U-46619, leukotriene D4, etc. For example, the desired compounds [I] wherein R^1 and R^2 are lower alkoxy group, R^3 is pyridyl group, N-alkyl-2(1 H)-pyridonyl group or N-(lower alkoxy-lower alkyl)-2(1 H)-pyridonyl group, a group of the formula: $-OR^4$ is hydroxy group or lower alkanoyloxy group, a group of the formula: $-OR^5$ is hydroxy group show 3 to 100 times as strong inhibitory activity on histamine-induced bronchoconstriction as theophylline.

Moreover, the desired compounds [I] of the present invention and pharmaceutically acceptable salts thereof hardly show any side effects on heart, and they show selectively bronchodilating activity as well as low-toxicity so that these compounds advantageously show high safety as medicaments. Although it is widely known that theophylline shows serious side effects on heart such as lowering blood pressure, palpitation, and the like, the desired compounds [I] of the present invention and pharmaceutically acceptable salts thereof do not show such side effects, but show excellent antiasthmatic activity.

Claims

1. A naphthalene derivative of the formula (1) :



[I]

wherein R^1 and R^2 are the same or different and are (1) hydrogen atom, (2) hydroxy group, (3) a cyclo-C_{3-6} alkyloxy group, (4) a C_{1-6} alkoxy group which may optionally be substituted by a group selected from hydroxy group, a C_{1-6}

alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group and phenyl group, or (5) both combine each other to form a C_{1-6} alkylenedioxy group, R^3 is a nitrogen-containing 6-membered heterocyclic group which may optionally be substituted by a group selected from a halogen atom, an alkoxy group and an alkyl group, in which these alkoxyl group and alkyl group may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{2-6} alkenyl group, cyano group, carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aminocarbonyl group, a di-C_{1-6} alkylamino group, a C_{2-6} alkanoyl group, phenyl group, furyl group, tetrahydrofuryl group and oxazolyl group, and groups of the formulae: $-OR^4$ and $-OR^5$ are the same or different and are a protected or unprotected hydroxy group, or a pharmaceutically acceptable salt thereof.

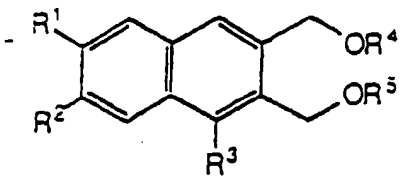
2. A compound according to claim 1 wherein R^3 is pyridyl group, N-oxypyridyl group, 2(1H)-pyridonyl group, 4,5-dihydro-3(2H)-pyridazinonyl group or 3(2H)-pyridazinonyl group, which may optionally be substituted by a group selected from a halogen atom, an alkoxy group and an alkyl group, in which these alkoxyl group and alkyl group may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{2-6} alkenyl group, cyano group, carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aminocarbonyl group, a di-C_{1-6} alkylamino group, a C_{2-6} alkanoyl group, phenyl group, furyl group, tetrahydrofuryl group and oxazolyl group.

3. A compound according to claim 1 or claim 2, wherein R^3 is pyridyl group, N-oxypyridyl group, 2(1H)-pyridonyl group, 4,5-dihydro-3(2H)-pyridazinonyl group or 3(2H)-pyridazinonyl group, which may optionally be substituted by a halogen atom, or 2-alkoxypyridyl group or N-alkyl-2(1H)-pyridonyl group, in which these alkoxyl group and alkyl group may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{2-6} alkenyl group, cyano group, carboxyl group, a C_{1-6} alkoxy-carbonyl group, carbamoyl group, a di-C_{1-6} alkylamino group, phenyl group, furyl group, tetrahydrofuryl group, oxazolyl group and oxo group.

4. A compound according to any one of the preceding claims, wherein the groups of the formulae: $-OR^4$ and $-OR^5$ are the same or different, and are hydroxy group which may optionally be protected by a group selected from a C_{1-6} alkyl group and a C_{2-6} alkanoyl group.

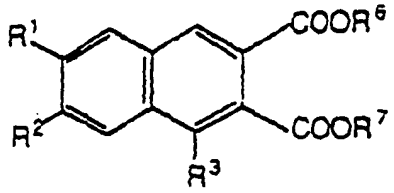
5. A compound according to any one of claims 3 or 4, wherein R^1 and R^2 are the same or different and are a C_{1-6} alkoxy group, R^3 is pyridyl group, an N-alkyl-2(1H)-pyridonyl group or N-(C_{1-6} alkoxy-C_{1-6} alkyl)-2(1H)-pyridonyl group, the group of the formula: $-OR^4$ is hydroxy group which may optionally be protected by a C_{2-6} alkanoyl group, and the group of the formula : $-OR^5$ is hydroxy group.

6. A process for preparing the compound of the formula (1):



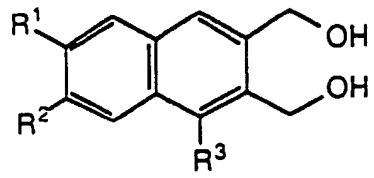
[I]

wherein R^1 and R^2 are the same or different and are (1) hydrogen atom, (2) hydroxy group, (3) a cyclo-C_{3-6} alkyloxy group, (4) a C_{1-6} alkoxy group which may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group and phenyl group, or (5) both combine each other to form a C_{1-6} alkylenedioxy group, R^3 is a nitrogen-containing 6-membered heterocyclic group which may optionally be substituted by a group selected from a halogen atom, an alkoxy group and an alkyl group, in which these alkoxyl group and alkyl group may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{2-6} alkenyl group, cyano group, carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aminocarbonyl group, a di-C_{1-6} alkylamino group, a C_{2-6} alkanoyl group, phenyl group, furyl group, tetrahydrofuryl group and oxazolyl group, and groups of the formulae: $-OR^4$ and $-OR^5$ are the same or different and are a protected or unprotected hydroxy group, or a pharmaceutically acceptable salt thereof, which comprises subjecting a compound of the formula (II):



[II]

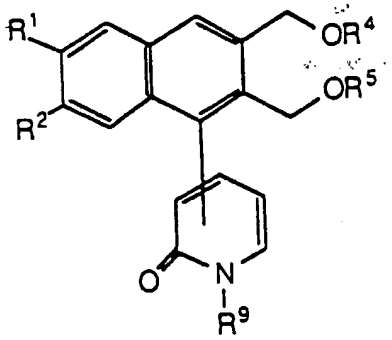
wherein groups of the formulae: -COOR^6 and -COOOR^7 are a free or esterified carboxyl group, and the other symbols are the same as defined above, or an internal anhydride thereof to reduction to give a compound of the formula (I-a):



[I-a]

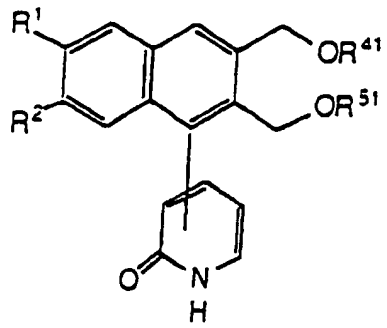
wherein the symbols are the same as defined above, if necessary, followed by protecting the 2- and/or 3-hydroxymethyl moieties of the compound (I-a), and further if necessary, converting the product into a pharmaceutically acceptable salt thereof.

7. A process for preparing a compoound of the formula (I-c):



[I-c]

wherein R^1 and R^2 are the same or different and are (1) hydrogen atom, (2) hydroxy group, (3) a cyclo-C_{3-6} alkyloxy group, (4) a C_{1-6} alkoxy group which may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group and phenyl group, or (5) both combine each other to form a C_{1-6} alkylenedioxy group, groups of the formulae: -OR^4 and -OR^5 are the same or different and are a protected or unprotected hydroxy group, and R^9 is a C_{1-6} alkyl group which may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{2-6} alkenyl group, cyano group, carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aminocarbonyl group, a di-C_{1-6} alkylamino group, a C_{2-6} alkanoyl group, phenyl group, furyl group, tetrahydrofuryl group and oxazolyl group, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of the formula (I-b_1)



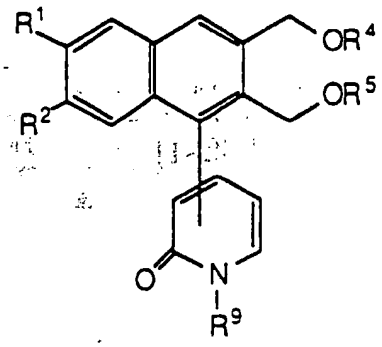
[I-b_1]

wherein groups of the formulae: -OR^{41} and -OR^{51} are a protected or unprotected hydroxy group, and the other symbols are the same as defined above, with a compound of the formula (III):

$$X - R^9 \qquad \text{(III)}$$

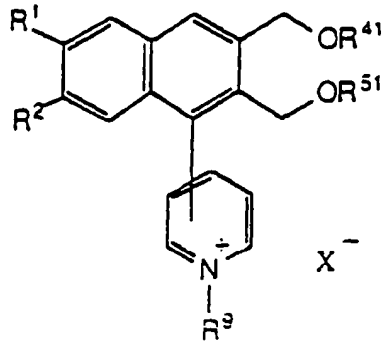
wherein X is a halogen atom, and R^9 is the same as defined above, and when the groups of the formulae: -OR^{41} and/or -OR^{51} are a protected hydroxy group, followed by removing the protecting group for said hydroxy groups, if necessary, protecting the 2 and/or 3-hydroxymethyl moieties of the product, and further if necessary, by converting the product into a pharmaceutically acceptable salt thereof.

8. A process for preparing a compound of the formula (I-c):



[I-c]

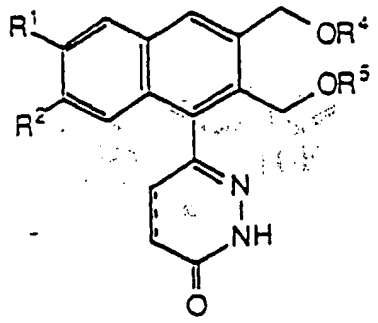
wherein R^1 and R^2 are the same or different and are (1) hydrogen atom, (2) hydroxy group, (3) a cyclo-C_{3-6} alkyloxy group, (4) a C_{1-6} alkoxy group which may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group and phenyl group, or (5) both combine each other to form a C_{1-6} alkylenedioxy group, groups of the formulae: -OR^4 and -OR^5 are the same or different and are a protected or unportected hydroxy group and R^9 is a C_{1-6} alkyl group which may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{2-6} alkenyl group, cyano group, carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aminocarbonyl group, a di-C_{1-6} alkylamino group, a C_{2-6} alkanoyl group, phenyl group, furyl group, tetrahydrofuryl group and oxazolyl group, or a pharmaceutically acceptable salt thereof, which comprises subjecting a compound of the formula (I-e_1):



[I-e$_1$]

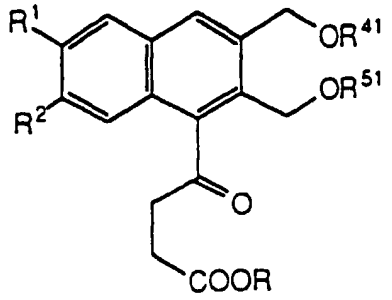
wherein the groups of the formulae: -OR^{41} and -OR^{51} are a protected or unprotected hydroxy group, and the other symbols are the same as defined above, to oxidation, and when the groups of the formulae: -OR^{41} and/or -OR^{51} are a protected hydroxy group, followed by removing a protecting group for said hydroxy group, if necessary, and further protecting the 2- and/or 3-hydroxymethyl moieties of the product, and if necessary, by converting the product into a pharmaceutically acceptable salt thereof.

9. A process for preparing a compound of the formula (I-h):



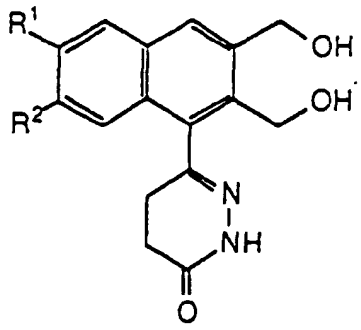
[I-h]

wherein R^1 and R^2 are the same or different, and are (1) hydrogen atom, (2) hydroxy group, (3) a cyclo-C_{3-6} alkyloxy group, (4) a C_{1-6} alkoxy group which may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group and phenyl group, or (5) both combine each other to form a C_{1-6} alkylenedioxy group, the groups of the formulae: -OR^4 and -OR^5 are the same or different and are a protected or unprotected hydroxy group, and the dotted line means a single bond or a double bond, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of the formula (IV):



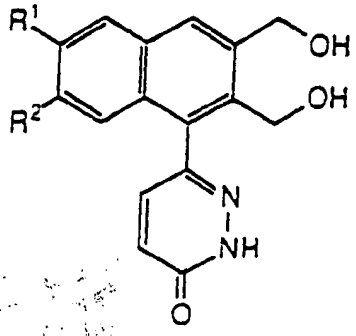
[IV]

wherein the groups of the formulae: -OR^{41} and -OR^{51} are a protected or unprotected hydroxy group, the group of the formula: -COOR is a free carboxyl group or an esterified carboxyl group, and the other symbols are the same as defined above, with hydrazine to give a compound of the formula (I-f):



[I-f]

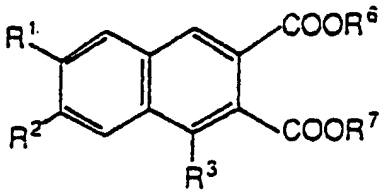
wherein the symbols are the same as defined above, if necessary, followed by subjecting the compound (I-f) to oxidation to give a compound of the formula (I-g):



[I-g]

wherein the symbols are the same as defined above, if necessary, protecting the 2- and/or 3-hydroxymethyl moieties of the product, and further by converting the product into a pharmaceutically acceptable salt thereof.

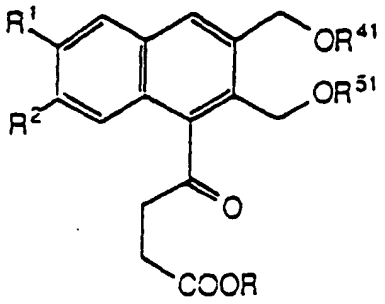
10. A compound of the formula (II):



[II]

wherein R^1 and R^2 are the same or different and are (1) hydrogen atom, (2) hydroxy group, (3) a cyclo-C_{3-6} alkyloxy group, (4) a C_{1-6} alkoxy group which may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group and phenyl group, or (5) both combine each other to form a C_{1-6} alkylenedioxy group,R^3 is a nitrogen-containing 6-membered heterocyclic group, which may optionally be substituted by a group selected from a halogen atom, an alkoxy group and an alkyl group, in which these alkoxyl group and alkyl group may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{2-6} alkenyl group, cyano group, carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aminocarbonyl group, a di-C_{1-6} alkylamino group, a C_{2-6} alkanoyl group, phenyl group, furyl group, tetrahydrofuryl group and oxazolyl group, and the groups of the formulae: -$COOR^6$ and -$COOR^7$ are a free carboxyl group or esterified carboxyl group, or an internal anhydride, or a salt thereof, except for the compound (II) wherein R^1 and R^2 are each a hydrogen atom, R^3 is piperidino group, R^6 and R^7 are each a methyl group.

11. A compound of the formula (IV):



[IV]

wherein R^1 and R^2 are the same or different and are (1) hydrogen atom, (2) hydroxy group, (3) a cyclo-C_{3-6} alkyloxy group, (4) a C_{1-6} alkoxy group which may optionally be substituted by a group selected from hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group and phenyl group, or (5) both combine each other to form a C_{1-6} alkylenedioxy group, and the groups of the formulae: -OR^{41} and -OR^{51} are a protected or unprotected hydroxy group, and a group of the formulae: -COOR is a free carboxyl group or esterified carboxyl group, or a salt thereof.

12. A compound according to claim 1, which is 1-[N-(2-methoxyethyl)-2(1H)-pyridon-4-yl]-2,3-bis (hydroxymethyl)-6,7-diethoxynaphthalene or a pharmaceutically acceptable salt thereof.

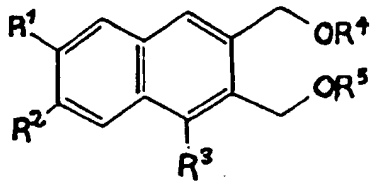
13. A compound according to claim 1, which is 1-[N-(2-methoxyethyl)-2(1H)-pyridon-4-yl]-2,3-bis (hydroxymethyl)-6-ethoxy-7-methoxynaphthalene or a pharmaceutical acceptable salt thereof.

14. A pharmaceutical composition which comprises as an active ingredient an effective amount of the compound as set forth in claim 1 in admixture with a pharmaceutically acceptable carrier or diluent.

15. Use of the compound as set forth in claim 1 for preparing a curing and/or prophylactic medicine for asthma.

Patentansprüche

1. Naphthalinderivat der Formel (1):



[I]

in der R^1 und R^2 gleich oder verschieden sind und (1) Wasserstoffatom, (2) Hydroxygruppe, (3) eine Cyclo-C_{3-6}-Alkyloxygruppe, (4) eine C_{1-6}-Alkoxygruppe, die wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe und Phenylgruppe, substituiert sein kann, sind oder (5) sich beide unter Bildung einer C_{1-6}-Alkylendioxygruppe miteinander verbinden; R^3 eine Stickstoff-haltige 6-gliedrige heterocyclische Gruppe ist, welche wahlweise durch eine Gruppe, ausgewählt unter einem Halogenatom, einer Alkoxygruppe und einer Alkylgruppe, substituiert sein kann, wobei diese Alkoxygruppe und diese Alkylgruppe wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkylthiogruppe, einer C_{2-6}-Alkenylgruppe, Cyanogruppe, Carboxylgruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer Aminocarbonylgruppe, einer Di-C_{1-6}-alkylaminogruppe, einer C_{2-6}-Alkanoykgruppe, Phenylgruppe, Furylgruppe, Tetrahydrofurylgruppe und Oxazolylgruppe, substituiert sein können; und die Gruppen der Formeln -OR^4 und -OR^5 gleich oder verschieden sind und jeweils eine geschützte oder ungeschützte Hydroxygruppe sind;
oder ein pharmazeutisch akzeptables Salz desselben.

2. Verbindung nach Anspruch 1, in der R^3 eine Pyridylgruppe, eine N-Oxypyridylgruppe, eine 2(1H)-Pyridonylgruppe,

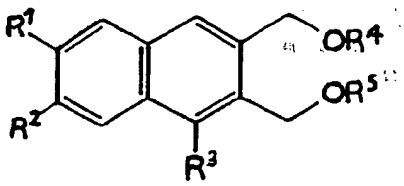
eine 4,5-Dihydro-3(2H)-pyridazinonylgruppe oder eine 3(2H)-Pyridazinonylgruppe ist, welche wahlweise durch eine Gruppe, ausgewählt unter einem Halogenatom, einer Alkoxygruppe und einer Alkylgruppe, substituiert sein kann, wobei diese Alkoxygruppe und diese Alkylgruppe wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-alkylthiogruppe, einer C_{2-6}-Alkenylgruppe, Cyanogruppe, Carboxylgruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer Aminocarbonylgruppe, einer Di-C_{1-6}-Alkylaminogruppe, einer C_{2-6}-Alkanoylgruppe, Phenylgruppe, Furylgruppe, Tetrahydrofurylgruppe und Oxazolylgruppe, substituiert sein können.

3. Verbindung nach Anspruch 1 oder Anspruch 2, in der R^3 eine Pyridylgruppe, eine N-Oxypyridylgruppe, eine 2(1H)-Pyridonylgruppe, eine 4,5-Dihydro-3(2H)-pyridazinonylgruppe oder eine 3(2H)-Pyridazinonylgruppe, welche wahlweise durch ein Halogenatom substituiert sein kann, oder eine 2-Alkoxypyridylgruppe oder eine N-Alkyl-2(1H)-pyridonylgruppe ist, in der diese Alkoxygruppe und diese Alkylgruppe wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkylthiogruppe, einer C_{2-6}-Alkenylgruppe, Cyanogruppe, Carboxylgruppe, einer C_{1-6}-Alkoxycarbonylgruppe, Carbamoylgruppe, einer Di-C_{1-6}-alkylaminogruppe, Phenylgruppe, Furylgruppe, Tetrahydrofurylgruppe, Oxazolylgruppe und Oxogruppe substituiert sein können.

4. Verbindung nach einem der vorangehenden Ansprüche, in der die Gruppen der Formeln $-OR^4$ und $-OR^5$ gleich oder verschieden sind und Hydroxygruppen sind, die wahlweise durch eine Gruppe, ausgewählt unter einer C_{1-6}-Alkylgruppe und einer C_{2-6}-Alkanoylgruppe, geschützt sein können.

5. Verbindung nach einem der Ansprüche 3 oder 4, in der R^1 und R^2 gleich oder verschieden sind und eine C_{1-6}-Alkoxygruppe sind; R^3 eine Pyridylgruppe, eine N-Alkyl-2(1H)-pyridonylgruppe oder eine N-(C_{1-6}-Alkoxy-C_{1-6}-alkyl)-2(1H)-pyridonylgruppe ist; die Gruppe der Formel $-OR^4$ eine Hydroxygruppe, die wahlweise durch eine C_{2-6}-Alkanoylgruppe geschützt sein kann, ist; und die Gruppe der Formel $-OR^5$ eine Hydroxygruppe ist.

6. Verfahren zur Herstellung der Verbindung der Formel (1):

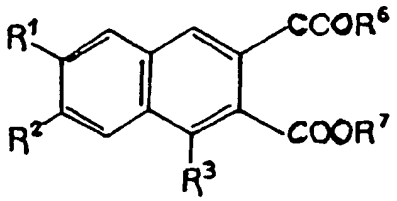


[I]

in der R^1 und R^2 gleich oder verschieden sind und (1) Wasserstoffatom, (2) Hydroxygruppe, (3) eine Cyclo-C_{3-6}-Alkyloxygruppe, (4) eine C_{1-6}-Alkoxygruppe, die wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe und Phenylgruppe, substituiert sein kann, sind oder (5) sich beide unter Bildung einer C_{1-6}-Alkylendioxygruppe miteinander verbinden; R^3 eine Stickstoff-haltige 6-gliedrige heterocyclische Gruppe ist, welche wahlweise durch eine Gruppe, ausgewählt unter einem Halogenatom, einer Alkoxygruppe und einer Alkylgruppe, substituiert sein kann, wobei diese Alkoxygruppe und diese Alkylgruppe wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkylthiogruppe, einer C_{2-6}-Alkenylgruppe, Cyanogruppe, Carboxylgruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer Aminocarbonylgruppe, einer Di-C_{1-6}-alkylaminogruppe, einer C_{2-6}-Alkanoylgruppe, Phenylgruppe, Furylgruppe, Tetrahydrofurylgruppe und Oxazolylgruppe, substituiert sein können; und die Gruppen der Formeln $-OR^4$ und $-OR^5$ gleich oder verschieden sind und eine geschützte oder ungeschützte Hydroxygruppe sind;

oder eines pharmazeutisch akzeptablen Salzes derselben,

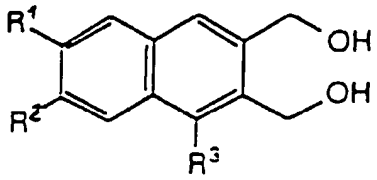
das ein Unterwerfen einer Verbindung der Formel (II):



[II]

in der Gruppen der Formeln -COOR^6 und -COOR^7 jeweils eine freie oder veresterte Carboxylgruppe sind, und die anderen Symbole wie die oben definiert sind,

oder eines internen Anhydrids derselben einer Reduktion unter Erhalt einer Verbindung der Formel (I-a):

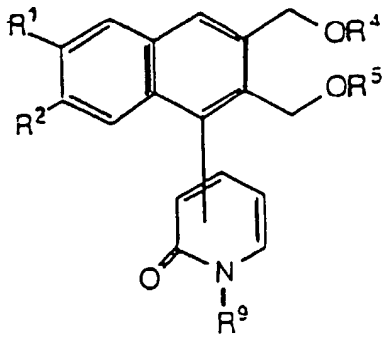


[I-a]

in der die Symbole wie oben definiert sind,

wenn notwendig, anschließendes Schützen der 2- und/oder 3-Hydroxymethylgruppen der Verbindung (I-a), und außerdem, wenn notwendig, Umwandeln des Produktes in ein pharmazeutisch akzeptables Salz desselben umfaßt.

7. Verfahren zur Herstellung einer Verbindung der Formel (I-c):

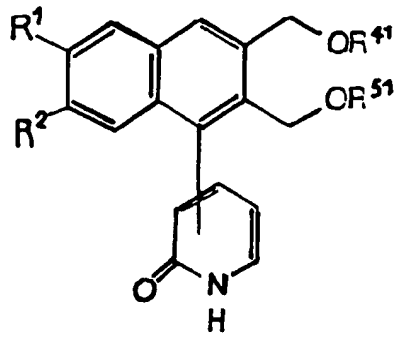


[I-c]

in der R^1 und R^2 gleich oder verschieden sind und (1) Wasserstoffatom, (2) Hydroxygruppe, (3) eine Cyclo-C_{3-6}-Alkyloxygruppe, (4) eine C_{1-6}-Alkoxygruppe sind, die wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe und Phenylgruppe, substituiert sein kann, sind, oder (5) sich beide unter Bildung einer C_{1-6}-Alkylendioxygruppe miteinander verbinden; die Gruppen der Formeln -OR^4 und -OR^5 gleich oder verschieden sind und eine geschützte oder ungeschützte Hydroxygruppe sind; und R^9 eine C_{1-6}-Alkylgruppe ist, welche wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkylthiogruppe, einer C_{2-6}-Alkenylgruppe, Cyanogruppe, Carboxylgruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer Aminocarbonylgruppe, einer Di-C_{1-6}-alkylaminogruppe, einer C_{2-6}-Alkanoylgruppe, Phenylgruppe, Furylgruppe, Tetrahydrofurylgruppe und Oxazolylgruppe, substituiert sein kann;

oder eines pharmazeutisch akzeptablen Salzes derselben,

das Umsetzen einer Verbindung der Formel (I-b_1)



[I-b_1]

worin die Gruppen der Formeln -OR^{41} und -OR^{51} jeweils eine geschützte oder ungeschützte Hydroxygruppe sind, und die anderen Symbole wie oben definiert sind,

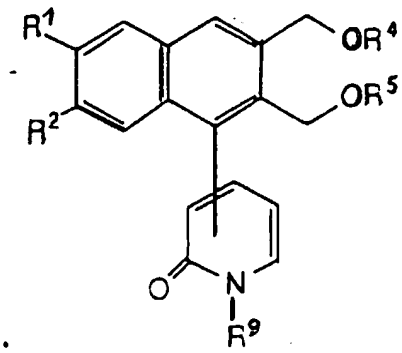
mit einer Verbindung der Formel (III):

$$X - R^9 \qquad \text{(III)}$$

worin X ein Halogenatom ist, und R^9 wie oben definiert ist,

und wenn die Gruppen der Formeln -OR^{41} und/oder -OR^{51} jeweils eine geschützte Hydroxygruppe sind, anschließendes Entfernen der Schutzgruppe für diese Hydroxygruppen, wenn notwendig, Schützen der 2-und/oder 3-Hydroxymethylgruppen des Produktes, und außerdem, wenn notwendig, Umwandeln des Produktes in ein pharmazeutisch akzeptables Salz desselben umfaßt.

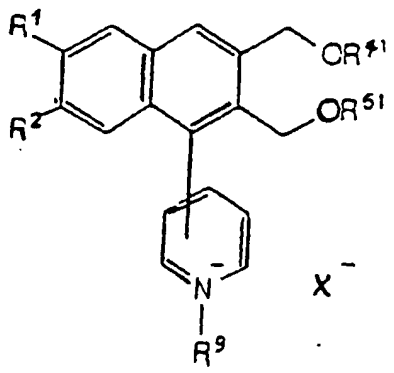
8. Verfahren zur Herstellung einer Verbindung der Formel (I-c):



[I-c]

in der R^1 und R^2 gleich oder verschieden sind und (1) Wasserstoffatom, (2) Hydroxygruppe, (3) eine Cyclo-C_{3-6}-Alkyloxygruppe, (4) eine C_{1-6}-Alkoxygruppe, welche wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe und Phenylgruppe, substituiert sein kann, sind oder (5) sich beide unter Bildung einer C_{1-6}-Alkylendioxygruppe miteinander verbinden; die Gruppen der Formeln -OR^4 und -OR^5 gleich oder verschieden sind und jeweils eine geschützte oder ungeschützte Hydroxygruppe sind; und R^9 eine C_{1-6}-Alkylgruppe ist, die wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkylthiogruppe, einer C_{2-6}-Alkenylgruppe, Cyanogruppe, Carboxylgruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer Aminocarbonylgruppe, einer Di-C_{1-6}-alkylaminogruppe, einer C_{2-6}-Alkanoylgruppe, Phenylgruppe, Furylgruppe, Tetrahydrofurylgruppe und Oxazolylgruppe, substituiert sein kann;

oder eines pharmazeutisch akzeptablen Salzes derselben, das ein Unterwerfen einer Verbindung der Formel (I-e_1):

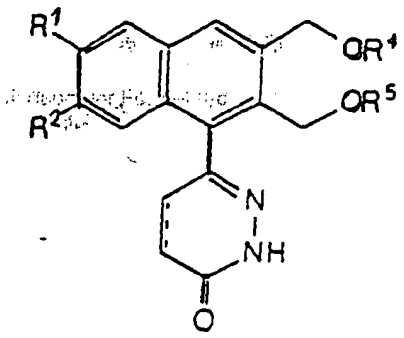


[I-e$_1$]

in der die Gruppen der Formeln -OR^{41} und -OR^{51} jeweils eine geschützte oder ungeschützte Hydroxygruppe sind, und die anderen Symbole wie oben definiert sind,

einer Oxidation, und wenn die Gruppen der Formeln -OR^{41} und/oder -OR^{51} jeweils eine geschützte Hydroxygruppe sind, anschließendes Entfernen der Schutzgruppe für die Hydroxygruppen, wenn notwendig, und außerdem Schützen der 2- und/oder 3-Hydroxymethylgruppen des Produktes, wenn notwendig, Umwandeln des Produktes in ein pharmazeutisch akzeptables Salz desselben umfaßt.

9. Verfahren zur Herstellung einer Verbindung der Formel (I-h):

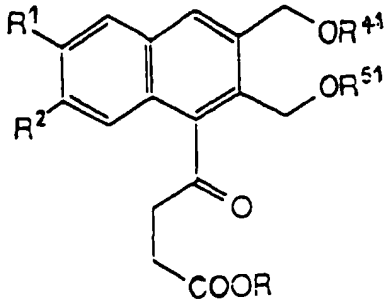


[I-h]

in der R^1 und R^2 gleich oder verschieden sind und (1) Wasserstoffatom, (2) Hydroxygruppe, (3) eine Cyclo-C_{3-6}-Alkyloxygruppe, (4) eine C_{1-6}-Alkoxygruppe, welche wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe und Phenylgruppe, substituiert sein kann, sind oder (5) sich beide unter Bildung einer C_{1-6}-Alkylendioxygruppe miteinander verbinden; die Gruppen der Formeln -OR^4 und -OR^5 gleich oder verschieden sind und jeweils eine geschützte oder ungeschützte Hydroxygruppe sind, und die gestrichelte Linie eine Einfachbindung oder Doppelbindung bezeichnet,

oder eines pharmazeutisch akzeptablen Salzes derselben,

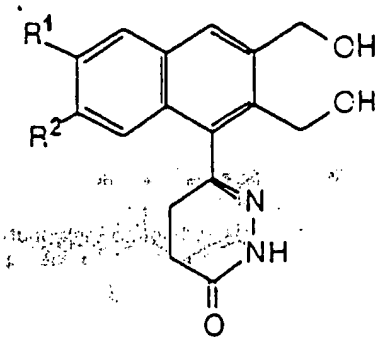
das eine Umsetzung einer Verbindung der Formel (IV):



[IV]

in der die Gruppen der Formeln -OR^{41} und -OR^{51} jeweils eine geschützte oder ungeschützte Hydroxygruppe sind, und die Gruppe der Formel -COOR eine freie Carboxylgruppe oder eine veresterte Carboxylgruppe ist, und die anderen Symbole wie oben definiert sind,

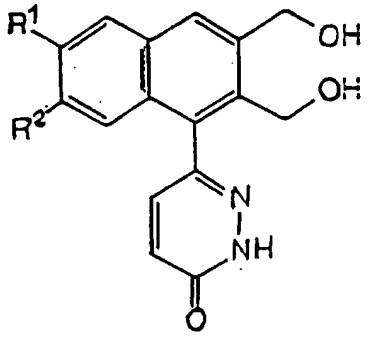
mit Hydrazin unter Bildung einer Verbindung der Formel (I-f):



[I-f]

in der die Symbole wie oben definiert sind,

wenn notwendig, anschließend ein Unterwerfen der Verbindung (I-f) einer Oxidation unter Erhalt einer Verbindung der Formel (I-g):

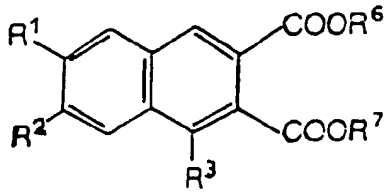


[I-g]

in der die Symbole wie oben definiert sind,

wenn notwendig, Schützen der 2- und/oder 3-Hydroxymethylgruppen des Produktes und ferner Umwandeln des Produktes in ein pharmazeutisch akzeptables Salz desselben umfaßt.

10. Verbindung der Formel (II):

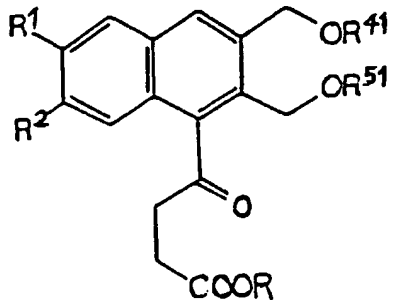


[II]

in der R^1 und R^2 gleich oder verschieden sind und (1) Wasserstoffatom, (2) Hydroxygruppe, (3) eine Cyclo-C_{3-6}-alkyloxygruppe, (4) eine C_{1-6}-Alkoxygruppe, welche wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe und Phenylgruppe, substituiert sein kann, sind oder (5) sich beide unter Bildung einer C_{1-6}-Alkylendioxygruppe miteinander verbinden; R^3 eine Stickstoff-haltige 6-gliedrige heterocyclische Gruppe ist, welche wahlweise durch eine Gruppe, ausgewählt unter einem Halogenatom, einer Alkoxygruppe und einer Alkylgruppe substituiert sein kann, wobei diese Alkoxygruppe und diese Alkylgruppe wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkyloxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkylthiogruppe, einer C_{2-6}-Alkenylgruppe, Cyanogruppe, Carboxylgruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer Aminocarbonylgruppe, einer Di-C_{1-6}-alkylaminogruppe, einer C_{2-6}-Alkanoylgruppe, Phenylgruppe, Furylgruppe, Tetrahydrofurylgruppe und Oxazolylgruppe, substituiert sein können und die Gruppen der Formeln -$COOR^6$ und -$COOR^7$ jeweils eine freie Carboxylgruppe oder eine veresterte Carboxylgruppe sind,

oder ein inneres Anhydrid oder ein Salz derselben, ausgenommen die Verbindung (II), in der R^1 und R^2 jeweils ein Wasserstoffatom sind, R^3 eine Piperidinogruppe ist, R^6 und R^7 jeweils eine Methylgruppe sind.

11. Verbindung der Formel (IV):



[IV]

in der R^1 und R^2 gleich oder verschieden sind und (1) Wasserstoffatom, (2) Hydroxygruppe, (3) eine Cyclo-C_{3-6}-alkyloxygruppe, (4) eine C_{1-6}-Alkoxygruppe, die wahlweise durch eine Gruppe, ausgewählt unter Hydroxygruppe, einer C_{1-6}-Alkoxygruppe, einer C_{1-6}-Alkoxy-C_{1-6}-alkoxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe und Phenylgruppe, substituiert sein kann, sind oder (5) sich beide unter Bildung einer C_{1-6}-Alkylendioxygruppe miteinander verbinden; und die Gruppen der Formeln -OR^{41} und -OR^{51} jeweils eine geschützte oder ungeschützte Hydroxygruppe sind, und eine Gruppe der Formel -COOR eine freie Carboxylgruppe oder eine veresterte Carboxylgruppe ist,

oder ein Salz derselben.

12. Verbindung nach Anspruch 1, die 1-[N-(2-Methoxyethyl)-2(1H)-pyridon-4-yl]-2,3-bis(hydroxymethyl)-6,7-diethoxynaphthalin oder ein pharmazeutisch akzeptables Salz desselben ist.

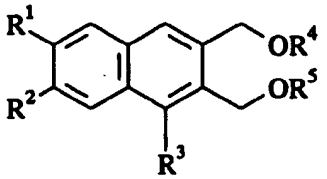
13. Verbindung nach Anspruch 1, die 1-[N-(2-Methoxyethyl)-2(1H)-pyridon-4-yl]-2,3-bis(hydroxymethyl)-6-ethoxy-7-methoxynaphtahlin oder ein pharmazeutisch akzeptables Salz desselben ist.

14. Pharmazeutische Zusammensetzung, die als aktives Ingrediens eine wirksame Menge der Verbindung, wie sie in Anspruch 1 definiert ist, im Gemisch mit einem pharmazeutisch akzeptablen Trägerstoff oder Verdünnungsmittel enthält.

15. Verwendung der Verbindung, wie sie in Anspruch 1 definiert ist, zur Herstellung eines heilenden und/oder prophylaktischen Arzneimittels für Asthma.

Revendications

1. Dérivé de naphtalène de formule (I) :



(I)

dans laquelle R^1 et R^2 sont les mêmes ou différents et représentent chacun (1) un atome d'hydrogène, (2) un groupe hydroxyle, (3) un groupe cycloalcoxy en C_3-C_6, (4) un groupe alcoxy en C_1-C_6 qui peut être facultativement substitué par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-carbonyle et un groupe phényle ou (5) les deux sont combinés l'un avec l'autre pour former un groupe alkylènedioxy en C_1-C_6, R^3 est un groupe hétérocyclique azoté à 6 chaînons qui peut être facultativement substitué par un reste choisi parmi un atome d'halogène, un groupe alcoxy et un groupe alkyle, où ces groupes alcoxyles et alkyles peuvent être facultativement substitués par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe alcényle en C_2-C_6, un groupe cyano, un groupe carboxyle, un groupe (alcoxy en C_1-C_6)-carbonyle, un groupe aminocarbonyle, un groupe di(alkyl en C_1-C_6)-amino, un groupe alcanoyle en C_2-C_6, un groupe phényle, un groupe furyle, un groupe tétrahydrofuryle et un groupe oxazolyle et les groupes de formules $-OR^4$ et $-OR^5$ sont les mêmes ou différents et représentent chacun un groupe hydroxyle protégé ou non, ou un de ses sels acceptables en pharmacie.

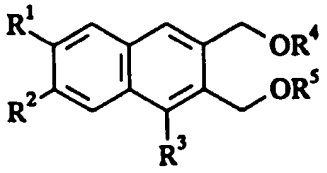
2. Composé selon la revendication 1, dans lequel R^3 est un groupe pyridyle, un groupe N-oxypyridyle, un groupe 2(1H)-pyridonyle, un groupe 4,5-dihydro-3(2H)-pyridazinonyle ou un groupe 3(2H)-pyridazinonyle, qui peut être facultativement substitué par un reste choisi parmi un atome d'halogène, un groupe alcoxy et un groupe alkyle, où ces alcoxyle et alkyle peuvent être facultativement substitués par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe alcényle en C_2-C_6, un groupe cyano, un groupe carboxyle, un groupe (alcoxy en C_1-C_6)-carbonyle, un groupe aminocarbonyle, un groupe di(alkyl en C_1-C_6)-amino, un groupe alcanoyle en C_2-C_6, un groupe phényle, un groupe furyle et un groupe tétrahydrofuryle et un groupe oxazolyle.

3. Composé selon la revendication 1 ou 2, dans lequel R^3 est un groupe pyridyle, un groupe N-oxypyridyle, un groupe 2(1H)-pyridonyle, un groupe 4,5-dihydro-3(2H)-pyridazinonyle ou un groupe 3(2H)-pyridazinonyle, qui peut être facultativement substitué par un atome d'halogène, ou un groupe 2-alcoxypyridyle ou un groupe N-alkyl-2(1H)-pyridonyle, où ces groupes alcoxyles et alkyles peuvent être facultativement substitués par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe alcényle en C_2-C_6, un groupe cyano, un groupe carboxyle, un groupe (alcoxy en C_1-C_6)-carbonyle, un groupe carbamoyle, un groupe di-(alkyl en C_1-C_6)amino, un groupe phényle, un groupe furyle, un groupe tétrahydrofuryle, un groupe oxazolyle et un groupe oxo.

4. Composé selon l'une quelconque des revendications précédentes, dans lequel les groupes de formules $-OR^4$ et $-OR^5$ sont les mêmes ou différents et sont chacun un groupe hydroxyle qui peut facultativement être protégé par un groupe choisi parmi un groupe alkyle en C_1-C_6 et un groupe alcanoyle en C_2-C_6.

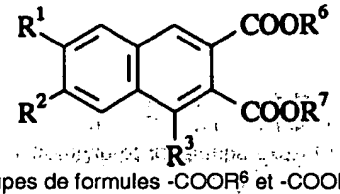
5. Composé selon la revendication 3 ou 4, dans lequel R^1 et R^2 sont les mêmes ou différents et sont chacun un groupe alcoxy en C_1-C_6, R^3 est un groupe pyridyle, un groupe N-alkyl-2(1H)-pyridonyle ou un groupe N-[(alcoxy en C_1-C_6)-alkyl en C_1-C_6]-2(1H)-pyridonyle, le groupe de formule $-OR^4$ est un groupe hydroxyle qui peut facultativement être protégé par un groupe alcanoyle en C_2-C_6 et le groupe de formule $-OR^5$ est un groupe hydroxyle.

6. Procédé pour préparer le composé de formule I:



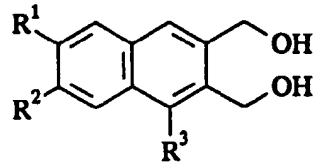
(I)

dans laquelle R^1 et R^2 sont les mêmes ou différents et représentent chacun (1) un atome d'hydrogène, (2) un groupe hydroxyle, (3) un groupe cycloalcoxy en C_3-C_6, (4) un groupe alcoxy en C_1-C_6 qui peut être facultativement substitué par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-carbonyle et un groupe phényle ou (5) les deux sont combinés l'un avec l'autre pour former un groupe alkylènedioxy en C_1-C_6, R^3 est un groupe hétérocyclique azoté à 6 chaînons qui peut être facultativement substitué par un reste choisi parmi un atome d'halogène, un groupe alcoxy et un groupe alkyle, où ces groupes alcoxyles et alkyles peuvent être facultativement substitués par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe alcényle en C_2-C_6, un groupe cyano, un groupe carboxyle, un groupe (alcoxy en C_1-C_6)-carbonyle, un groupe aminocarbonyle, un groupe di(alkyl en C_1-C_6)-amino, un groupe alcanoyle en C_2-C_6, un groupe phényle, un groupe furyle, un groupe tétrahydrofuryle et un groupe oxazolyle et les groupes de formules $-OR^4$ et $-OR^5$ sont les mêmes ou différents et représentent chacun un groupe hydroxyle protégé ou non, ou un de ses sels acceptables en pharmacie, qui comprend les étapes suivantes : réduction d'un composé de formule (II):



(II)

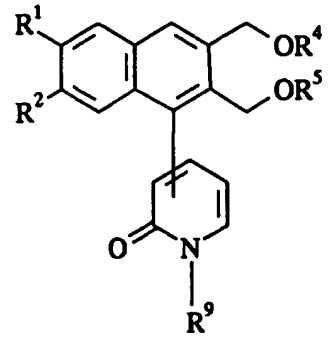
dans laquelle les groupes de formules $-COOR^6$ et $-COOR^7$ sont chacun un groupe carboxyle libre ou estérifié et les autres symboles sont tels que définis ci-dessus, ou de son anhydride interne pour donner un composé de formule (I-a):



(I-a)

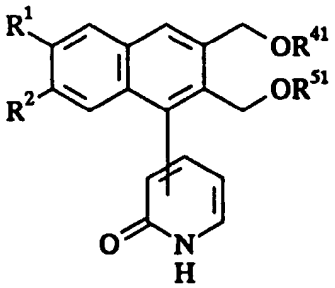
dans laquelle les symboles sont tels que défini ci-dessus ; puis, si nécessaire, protection des restes 2- et/ou 3-hydroxyméthyles du composé (I-a) ; et ensuite, si nécessaire, conversion du produit en un de ses sels acceptables en pharmacie.

7. Procédé pour préparer un composé de formule (I-c) :



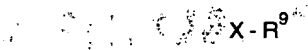
(I-c)

dans laquelle R^1 et R^2 sont les mêmes ou différents et représentent chacun (1) un atome d'hydrogène, (2) un groupe hydroxyle, (3) un groupe cycloalcoxy en C_3-C_6, (4) un groupe alcoxy en C_1-C_6 qui peut être facultativement substitué par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-cubonyle et un groupe phényle ou (5) les deux sont combinés l'un avec l'autre pour former un groupe alkylènedioxy en C_1-C_6, les groupes de formules $-OR^4$ et $-OR^5$ sont les mêmes ou différents et représentent chacun un groupe hydroxyle protégé ou non et R^9 est un groupe alkyle en C_1-C_6 qui peut être facultativement substitué par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe alcényle en C_2-C_6, un groupe cyano, un groupe carboxyle, un groupe (alcoxy en C_1-C_6)-carbonyle, un groupe aminocarbonyle, un groupe di-(alkyl en C_1-C_6)amino, un groupe alcanoyle en C_2-C_6, un groupe phényle, un groupe furyle, un groupe tétrahydrofuryle et un groupe oxazolyle ou un de ses sels acceptables en pharmacie, qui comprend des étapes suivantes : réaction d'un composé de formule (I-b_1) :



(I-b_1)

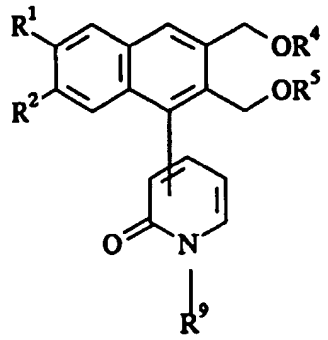
dans laquelle les groupes de formules $-OR^{41}$ et $-OR^{51}$ sont chacun un groupe hydroxyle protégé ou non et les autres symboles sont tels que définis ci-dessus, avec un composé de formule (III) :



(III)

dans laquelle X est un atome d'halogène et R^9 est tel que défini ci-dessus et lorsque les groupes de formule $-OR^{41}$ et/ou $-OR^{51}$ sont des groupes hydroxyles protégés, séparation du groupe protecteur desdits groupes hydroxyles ; si nécessaire, protection des restes 2-et/ou 3-hydroxyméthyles du produit ; et si nécessaire encore, conversion du produit en un de ses sels acceptables en pharmacie.

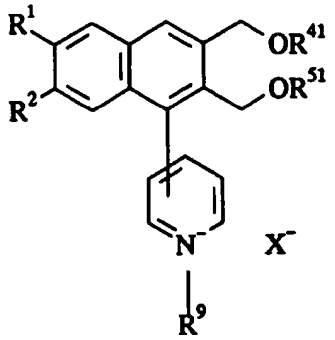
8. Procédé pour préparer un composé de formule (I-c) :



(I-c)

dans laquelle R^1 et R^2 sont les mêmes ou différents et représentent chacun (1) un atome d'hydrogène, (2) un groupe hydroxyle, (3) un groupe cycloalcoxy en C_3-C_6, (4) un groupe alcoxy en C_1-C_6 qui peut facultativement être substitué par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-carbonyle et un groupe phényle ou (5) les deux sont combinés l'un avec l'autre pour former un groupe alkylènedioxy en C_1-C_6, les groupes de formules $-OR^4$ et $-OR^5$ sont les mêmes ou différents et sont chacun un groupe hydroxyle substitué ou non et R^9 est un groupe alkyle en C_1-C_6 qui peut être facultativement substitué par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe alcényle en C_2-C_6, un groupe cyano, un groupe carboxyle, un groupe (alcoxy en C_1-C_6)-carbonyle, un groupe aminocarbonyle, un groupe

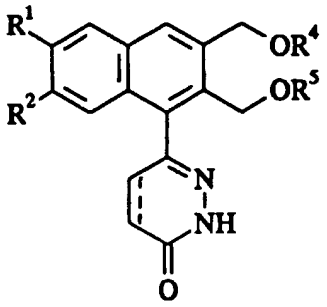
di(alkyl en C_1-C_6)-amino, un groupe alcanoyle en C_2-C_6, un groupe phényle, un groupe furyle, un groupe tétrahydrofuryle et un groupe oxazolyle, ou un de ses sels acceptables en pharmacie, qui comprend les étapes suivantes : oxydation d'un composé de formule (I-e_1) :



(I-e_1)

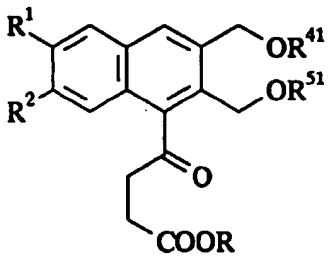
dans laquelle les groupes de formule -OR^{41} et -OR^{51} représentent chacun un groupe hydroxyle protégé ou non et les autres symboles sont tels que définis ci-dessus et ensuite, lorsque les groupes de formule -OR^{41} et/ou -OR^{51} sont un groupe hydroxyle protégé, séparation si nécessaire du groupe protecteur dudit groupe hydroxyle, et ensuite protection des restes 2- et/ou 3-hydroxyméthyle du produit et, si nécessaire, ensuite, conversion du produit en un de sels acceptables en pharmacie.

9. Procédé pour préparer un composé de formule (I-h) :



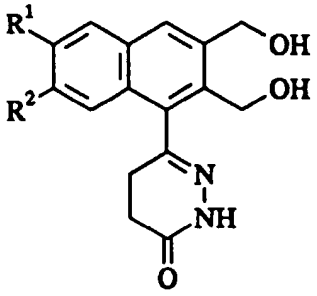
(I-h)

dans laquelle R^1 et R^2 sont les mêmes ou différents et représentent chacun (1) un atome d'hydrogène, (2) un groupe hydroxyle, (3) un groupe cycloalcoxy en C_3-C_6, (4) un groupe alcoxy en C_1-C_6 qui peut être facultativement substitué par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-carbonyle et un groupe phényle ou (5) les deux sont combinés l'un avec l'autre pour former un groupe alkylènedioxy en C_1-C_6, les groupes de formules -OR^4 et -OR^5 sont les mêmes ou différents et représentent chacun un groupe hydroxyle protégé ou non, et le trait interrompu désigne une liaison simple ou une liaison double, ou un de ses sels acceptables en pharmacie, qui comprend les étapes suivantes : réaction d'un composé de formule (IV) :



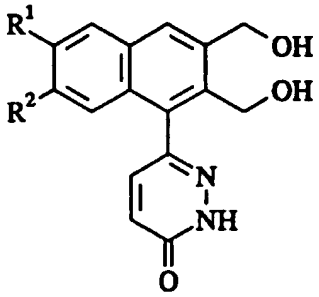
(IV)

dans laquelle les groupes de formules -OR^{41} et -OR^{51} sont chacun un groupe hydroxyle protégé ou non, le groupe de formule -COOR est un groupe carboxyle libre ou un groupe carboxyle estérifié et les autres symboles sont tels que définis ci-dessus, avec l'hydrazine pour donner un composé de formule (I-f) :



(I-f)

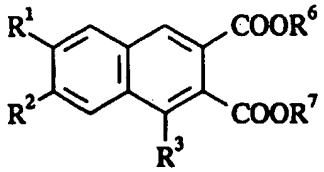
dans laquelle les symboles sont tels que définis ci-dessus ; si nécessaire, oxydation du composé (I-f) pour donner un composé de formule (I-g) :



(I-g)

les symboles sont tels que définis ci-dessus ; si nécessaire, protection des restes 2-et/ou 3-hydroxyméthyles du produit ; et ensuite de conversion du produit en un de sels acceptables en pharmacie.

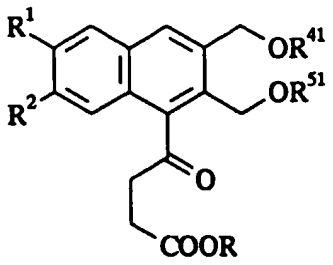
10. Composé de formule (II) :



(II)

dans laquelle R^1 et R^2 sont les mêmes ou différents et représentent chacun (1) un atome d'hydrogène, (2) un groupe hydroxyle, (3) un groupe cycloalcoxy en C_3-C_6, (4) un groupe alcoxy en C_1-C_6 qui peut être facultativement substitué par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-carbonyle et un groupe phényle ou (5) les deux sont combinés l'un avec l'autre pour former un groupe alkylènedioxy en C_1-C_6, R^3 est un groupe hétérocyclique azoté à 6 chaînons qui peut être facultativement substitué par un reste choisi parmi un atome d'halogène, un groupe alcoxy et un groupe alkyle, où ces groupes alcoxyles et alkyles peuvent être facultativement substitués par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe alcényle en C_2-C_6, un groupe cyano, un groupe carboxyle, un groupe (alcoxy en C_1-C_6)-carbonyle, un groupe aminocarbonyle, un groupe di(alkyl en C_1-C_6)-amino, un groupe alcanoyle en C_2-C_6, un groupe phényle, un groupe furyle, un groupe tétrahydrofuryle et un groupe oxazolyle, et les groupes de formules -$COOR^6$ et -$COOR^7$ sont chacun un groupe carboxyle libre ou un groupe carboxyle estérifié, ou son anhydride interne ou un de ses sels, sauf pour le composé (II) dans lequel R^1 et R^2 sont chacun un atome d'hydrogène, R^3 est un groupe pipéridino et R^6 et R^7 sont chacun un groupe méthyle.

11. Composé de formule (IV) :



(IV)

dans laquelle R^1 et R^2 sont les mêmes ou différents et représentent chacun (1) un atome d'hydrogène, (2) un groupe hydroxyle, (3) un groupe cycloalcoxy en C_3-C_6, (4) un groupe alcoxy en C_1-C_6 qui peut être facultativement substitué par un reste choisi parmi un groupe hydroxyle, un groupe alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-alcoxy en C_1-C_6, un groupe (alcoxy en C_1-C_6)-carbonyle et un groupe phényle ou (5) les deux sont combinés l'un avec l'autre pour former un groupe alkylènedioxy en C_1-C_6 et les groupes de formules $-OR^{41}$ et $-OR^{51}$ sont chacun un groupe hydroxyle protégé ou non et le groupe de formule -COOR est un groupe carboxyle libre ou un groupe carboxyle estérifié, ou un de ses sels.

12. Composé selon la revendication 1, qui est le 1-[N-(2-méthoxyéthyl)-2(1H)-pyridone-4-yl]-2,3-bis(hydroxyméthyl)-6,7diéthoxynaphtalène ou un de ses sels acceptables en pharmacie.

13. Composé selon la revendication 1, qui est le 1-[N-(2-méthoxyéthyl)-2(1H)-pyridone-4-yl]-2,3-bis(hydroxyméthyl)-6-éthoxy-7-méthoxynaphtalène ou un de ses sels acceptables en pharmacie.

14. Composition pharmaceutique, qui comprend comme ingrédient actif une quantité efficace du composé selon la revendication 1 en mélange avec un support ou diluant acceptable en pharmacie.

15. Utilisation du composé selon la revendication 1, pour la préparation d'un médicament pour le traitement et/ou la prophylaxie de l'asthme.